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DRUG PRODUCTS

Bioequivalence Requirements and In Vivo Bioavailability Procedures

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER D—DRUGS FOR HUMAN USE

[Docket No. 75N-0050]

PART 314—NEW DRUG APPLICATIONS

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

Procedures for Establishing a Bioequivalence Requirement

The Food and Drug Administration (FDA) is issuing final regulations defining certain terms relating to bioequivalence and setting forth procedures for establishing a bioequivalence requirement. These regulations are effective on February 7, 1977.

In the FEDERAL REGISTER of June 20, 1975 (40 FR 26164), the Commissioner of Food and Drugs proposed procedures for establishing a bioequivalence requirement when there is evidence that drug products containing the same active drug ingredient or therapeutic moiety and intended to be used interchangeably for the same therapeutic effect are not or might not be bioequivalent drug products. The Commissioner also proposed to define certain terms relating to bioequivalence and to amend the regulations to specify that failure to submit required bioavailability or bioequivalence data is reason for refusal to approve, or reason to withdraw approval of, a new drug application (NDA). Interested persons were invited to submit comments regarding the proposed regulations on or before August 4, 1975. In response to requests, the Commissioner extended the comment period to September 19, 1975, notice of which was published in the FEDERAL REGISTER of August 15, 1975 (40 FR 34407).

The Commissioner received 68 written comments regarding the proposed regulations. The comments were from individuals, trade and professional associations, pharmaceutical manufacturers, and Federal and State agencies. All of the comments may be seen in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, between the hours of 9 a.m. and 4 p.m., Monday through Friday.

After reviewing the comments and the proposed regulations, the Commissioner concludes that the proposed regulations should be reorganized. He believes that the procedures for establishing a bioequivalence requirement proposed in § 320.3 are too complex to be contained in only one section of the Code of Federal Regulations. Therefore, in the final regulations he is rearranging and redesignating proposed § 320.3 as §§ 320.50 through 320.62 and placing them in new Subpart C—Bioequivalence Requirements. This action will assure that the procedures for establishing a bioequivalence requirement are easier to find, read, and understand.

To aid the reader, the following table is provided to show the relationship of the final regulations to those proposed in § 320.3.

Proposed section	*Final section*
320.3(a)	320.51(a)
320.3(b)(1)-(6)	320.52
320.3(b)(7)	320.51(a)(3)
320.3(c)	320.51(a)-(b)
320.3(c)(1)-(5)	320.54
320.3(d)	320.51(a)
320.3(e)	320.55
320.3(f)	320.57
320.3(g)	320.58(a)
320.3(h)	320.58(b)
320.3(i)	320.58(c)
320.3(j)	320.58(d)
320.3(k)	320.58(e)
320.3(l)	320.56
320.3(m)	320.59
320.3(n)	320.51(d)
320.3(o)	320.60
320.3(p)	320.61
320.3(q)	320.62

The substantive comments received and the Commissioner's conclusions based on his evaluation of these comments are discussed below.

GENERAL

1. Thirty-nine comments from consumers, labor unions, and an association of retired persons expressed the opinion that the proposed regulations, if made final, would require physicians to prescribe drugs by generic name rather than by trade name and thus reduce the cost of prescription drugs. Thirty-eight of these comments supported a requirement that physicians prescribe by generic name; one comment opposed such a requirement.

The Commissioner advises that these bioequivalence regulations are not intended to, and do not, require a physician to prescribe any drug product by its generic name. The intent of the bioequivalence regulations is to assure that all drug products that are intended to be used interchangeably and that have a known or potential bioequivalence problem are identified and adequately manufactured and tested to assure that they are bioequivalent. The FDA, in approving a drug product for marketing, assures that the drug product is safe and effective for its labeled indications for use and meets all applicable standards of identity, strength, quality, and purity. The purpose of the bioequivalence regulations is to assure that, where necessary, these standards include a bioequivalence requirement.

2. One comment stated that the proposed regulations should not be implemented since they are unnecessary and would be destructive to the present method by which drugs are discovered, prescribed by doctors, and used by patients. The comment added that bioequivalence is an inadequately defined concept that may be used to establish a reckless system of equivalence whereby unequal drug products become equal and thereby interfere with the physician's freedom to utilize his trained judgment in the choice of drugs.

The Commissioner does not agree that bioequivalence is an inadequately defined concept whereby unequal drug products become equal, or that the proposed regulations will interfere with the physician's right or ability to choose appropriate drug therapy. The Commissioner recognizes that much of the variability in patient response to drug therapy classically has been attributed to patient variability rather than to drug product variability. Advances in pharmaceutical technology have made bioequivalence a most precise and reproducible method of determining drug product variability. These bioequivalence techniques are not inadequately defined or reckless concepts. They are scientifically valid methods of comparing different drug products as well as different batches of the same drug product. The Commissioner believes that the actions he is taking to assure bioequivalence of marketed drug products will enhance the physician's ability to choose appropriate drug therapy, because the physician will be assured that the product he selects will perform with greater consistency. The Commissioner also believes that information regarding drug product absorption, metabolism, and excretion can be constructive in revising the directions for use in the labeling and thereby provide for better patient care.

3. One comment stated that the proposed regulations exceed statutory authority, contravene the intent of Congress, and should not be finalized. The comment stated that there is no statutory basis for requiring bioequivalence evidence, that such evidence of relative comparability goes beyond the intent of Congress to assure that drugs are safe and effective, and that the legislative history expressly ruled out a requirement for a showing of relative effectiveness of a drug.

The bioequivalence regulations are not an attempt to equate evidence of bioequivalence with evidence of relative therapeutic effectiveness. All drug products are required under the Federal Food, Drug, and Cosmetic Act to meet appropriate standards to assure that they have their purported identity, strength, quality, and purity. Traditionally, these standards have used physical and chemical tests to characterize a drug product. With the development of the science of biopharmaceutics and pharmacokinetics, however, it is now possible to characterize a drug product more fully by determining its biological availability. Therefore, standards for certain drug products should be amended to include bioequivalence requirements. The Commissioner believes that the bioequivalence regulations are consistent with the intent of Congress to assure that drug products that contain the same active drug ingredient or therapeutic moiety and are intended to be used interchangeable meet the same standards.

4. One comment stated that the use of notice and comment rulemaking to establish a bioequivalence requirement for particular therapeutic moieties is procedurally improper. The comment alleged that such requirements may be imposed on new drugs only through adjudicatory procedures, and the proposed regulations should be amended to provide for the imposition of a bioequivalence requirement only after opportunity

for a hearing on the issuance of a declaratory order under the new drug provisions of the Federal Food, Drug, and Cosmetic Act.

The Commissioner does not agree with this comment. He believes that adjudicatory hearings are not appropriate for agency decisionmaking regarding the establishment of a bioequivalence requirement. The establishment of a bioequivalence requirement will ordinarily involve complex scientific and medical issues of general applicability that can be resolved more appropriately in the notice and comment rulemaking procedures. The legality of the rulemaking approach to drug regulation has been upheld by the Supreme Court ("Weinberger *v.* Hynson, Wescott & Dunning", 412 U.S. 609 (1973)). The Commissioner may, however, in his discretion, also subject any proposed bioequivalence requirement for a particular drug to an informal public hearing or a formal evidentiary public hearing, where such a procedure would contribute to resolution of the issues.

5. One comment objected to the assertion in the preamble that section 704 of the act (21 U.S.C. 374) authorizes the agency to require manufacturers to submit records and reports and information regarding bioequivalence. The comment argued that section 704, by its plain terms, precludes any such construction and the proposed regulations predicated thereon should be withdrawn.

Section 704 of the act provides that establishments that process prescription drug products are subject to FDA inspection, including review of certain records to determine compliance with the act and regulations. As noted in the preamble to the proposal, section 704(a) of the act distinguishes between physical entry of an establishment for inspection of the premises, and inspection of records that are maintained by an establishment. Physical entry is not required to inspect records, which are readily removable from the establishment. In the Commissioner's opinion, the law presently permits the adoption of a requirement for submission of these records directly to FDA, rather than requiring agency representatives to visit each facility to obtain such records. The Commissioner believes that submission of records directly to FDA presents no undue hardship for an establishment and is an effective, practical, and efficient procedure for obtaining certain information consistent with FDA's inspection authority. In addition, this approach may ease the burden of compliance by permitting a firm to assemble and submit the information to FDA in a reasonable period of time, rather than responding immediately when an FDA investigator arrives at the door of the establishment.

6. Two comments stated that, in their view, it is manifest that the Commissioner intends to establish a bioequivalence requirement in lieu of the need to file an NDA under section 505(b) of the act (21 U.S.C. 355(b)). The comment stated that such a policy is unlawful and in contravention of the dictates of section 505 of the act and the intent of Congress in requiring premarket approval of new drugs.

The Commissioner advises that establishment of a bioequivalence requirement does not relieve any manufacturer of the need to file a new drug application. If a bioequivalence requirement is established for a drug product that is a "new drug" as defined in section 201(p) of the act (21 U.S.C. 321(p)), each manufacturer will be required to submit a full or abbreviated NDA or supplemental application containing evidence that the drug product complies with the bioequivalence requirement. Evidence of bioequivalence will be in addition to evidence that the drug product is safe and effective for its intended use.

7. One comment expressed concern with the assumption that drug products that are bioequivalent are therefore equally safe. The comment explained that it is clear that two formulations of the same therapeutic moiety that demonstrate in vitro bioequivalence may have dramatically differing results when used in man. The comment added that even proven evidence of bioequivalence under proposed § 320.3 is no guarantee of safety.

Evidence of bioequivalence is only one test of equivalent safety and effectiveness among different drug products containing the same active drug ingredient or therapeutic moiety. Other factors that may affect the safety and effectiveness of different drug products containing the same active drug ingredient or therapeutic moiety include similarity of or differences between inactive ingredients; compliance of the manufacturing process with current good manufacturing practice; conformity with compendial or other standards of identity, strength, quality, and purity; and adequacy of drug product labeling. These factors are regulated through mechanisms other than the bioequivalence requirements. The Commissioner believes that if two or more drug products not presenting a bioequivalence problem contain identical amounts of the same active drug ingredient or therapeutic moiety in the same dosage form, are both manufactured in compliance with current good manufacturing practice, both contain inactive ingredients generally recognized as safe and suitable for the drug product formulation, both meet compendial or other standards of identity, strength, quality, and purity and are both adequately labeled, it is reasonable to assume that these products will be of equivalent safety and effectiveness. Moreover, if one of these products has been shown in adequate and well-controlled clinical trials to be safe and effective for its intended uses, there is no justification for requiring clinical trials to establish the safety and effectiveness of the second product in the absence of reasonable grounds for believing that the two products will not be of equivalent safety and effectiveness. It is neither feasible, nor in the interest of the public health, nor a productive use of scarce resources to require costly duplication of these tests.

8. One comment, noting that the preamble to the proposed regulation states that efforts should be made to develop in vitro tests that will be valid predictors of bioequivalence, stated that this opinion should be expanded to include a definition of in vitro tests that are correlated with in vivo data.

As stated in the preamble to the proposal, the Commissioner believes that the solution to a bioequivalence problem is to develop an in vitro bioequivalence standard that has been correlated with in vivo data. If, however, an in vitro bioequivalence standard does not exist, he believes that a solution to a bioequivalence problem is, where practicable, in vitro testing using a method specified by FDA that has not been correlated with in vivo data. This requirement would be imposed only until an in vitro bioequivalence standard that has been correlated with in vivo data is available. The relevant in vitro test will be defined in the individual bioequivalence requirement when the latter is issued.

9. One comment stated that the proposed bioequivalence requirements would force many of the smaller firms to cease selling generic products because of the cost involved in meeting these requirements. The comment added that bioequivalence requirements should be limited to the few cases where slight differences in the drug products constitute a substantial hazard to the public health.

The Commissioner is of the opinion that cost considerations cannot be the prime factor in determining whether to establish a bioequivalence requirement for certain drug products. A bioequivalence requirement would only be imposed, however, when bioinequivalence may have therapeutic significance. He believes, moreover, that bioequivalence can be determined for many drug products using less costly in vitro methodology. The Commissioner anticipates that in vivo testing will generally be limited to those drug products for which (a) there is well-documented evidence of therapeutic failure or bioinequivalence in drug products used for treatment of a serious disease, (b) careful dosage titration and patient monitoring is essential for safe and effective use, and (c) an in vitro bioequivalence standard, i.e., one that has been correlated with in vivo data, is unavailable.

10. One comment inquired as to how FDA will do in vivo and/or in vitro testing to assure bioequivalence. The comment stated that perhaps the agency could make use of university scientists who have no vested interest in the products in question to test these products for bioequivalence.

The Commissioner advises that the primary responsibility for performing in vivo and in vitro bioequivalence testing of a drug product rests with its manufacturer. The FDA will continue to do studies to improve existing methodology and specifications relating to bioequivalence and to test samples of marketed

drug products to assure the bioequivalence of these products. This testing will be done both in-house and through grants and contracts to competent university scientists and other appropriate investigators.

11. Several comments objected to what they consider to be the inherent assumption in the proposal that no prescription drug products except those listed in the preamble have a bioequivalence problem. The comment stated that FDA has failed to produce any valid scientific evidence to back up this assumption of equivalence.

The Commissioner advises that the proposed regulations were not based on the inherent assumption that only the prescription drug products listed in the preamble have a bioequivalence problem. The proposed regulations under § 320.3 (b) listed factors that the Commissioner would consider in determining whether there is a bioequivalence problem that requires the establishment of a bioequivalence requirement. Using these criteria, the Commissioner made a tentative finding that the drug products listed in the preamble had a known or potential bioequivalence problem. The purpose of the list was to generate public understanding of how FDA intends to apply the factors set forth in proposed § 320.3(b) to identify drug products for which a bioequivalence requirement should be established. Although an attempt was made to identify each drug product with a known or potential bioequivalence problem, the Commissioner recognizes that the list may omit some drug products with a known or potential bioequivalence problem. Likewise, the Commissioner emphasizes that a drug product's inclusion on the list does not necessarily imply that FDA has positive evidence of bioinequivalence among the various brands of the drug product.

12. One comment questioned the statement in the preamble to proposed § 320.3 that the Commissioner believes that relatively few of the marketed drug products meeting current in vitro standards and current good manufacturing practices will be found to have medically significant bioequivalence problems. The comment noted that the lengthy list of drug products in the preamble suggests more than a few potential bioequivalence problems.

In paragraph 11, the Commissioner emphasizes that a drug product's inclusion on the list does not necessarily imply that FDA has positive evidence of bioinquivalence among the various brands of the drug product. In compiling the list, FDA took a conservative approach. Therefore, a drug product was included on the list if, in FDA's opinion, there was any suspicion that the drug product had a known or potential bioequivalence problem or was a member of a class of drug products for which there was suspicion that at least one member of the class had a known or potential bioequivalence problem. The Commissioner is of the opinion that, as evidence of bioinequivalence is closely examined, few of the drug products listed will be determined to have well-documented, medically significant bioequivalence problems. A "medically significant bioequivalence problem" is one that would result in therapeutic failure or a hazard to a patient if different brands of the same drug product or different batches of the same brand are not bioequivalent. The Commissioner believes that a determination of bioequivalence is most critical in a drug product that has a narrow therapeutic-toxicity dosage range and requires careful patient titration and monitoring for safe and effective use.

13. Two comments objected to the list of drug products included in the preamble and identified as having known or potential bioequivalence problems. The comment added that the list is arbitrary, and, contrary to a statement made in the preamble, does not provide adequate information to manufacturers to assemble data and conduct bioequivalence studies in anticipation of a bioequivalence requirement. Several comments suggested that the list be amended to include additional drug products.

In responding to the comment in paragraph 11 of this preamble, the Commissioner acknowledges that the list of drug products may omit some drug products with a known or potential bioequivalence problem. The Commissioner does not agree that the list is arbitrary. The drug products listed were selected by the Commissioner using the factors proposed in § 320.3(b). The purpose of the list was to alert persons marketing a drug product on the list that, on the basis of an in-house review of data available to FDA, the Commissioner is concerned that the product has a bioequivalence problem and he will likely propose to establish a bioequivalence requirement for the drug product. At the time the Commissioner proposes a bioequivalence requirement, he will document the data to support the requirement. These persons, therefore, can rely on this advance information if they wish to conduct bioequivalence studies in anticipation of the establishment of the requirement by rule making.

The majority of the drug products listed in the preamble and identified as having a known or potential bioequivalence problem were drug products evaluated as effective for at least one indication in the Drug Efficacy Study. The Commissioner advises that FDA will continue to require the submission of bioavailability data in a full or abbreviated NDA for any of these products and for identical, related, or similar drug products. This policy is being codified in § 320.22(c) (21 CFR 320.22(c)) of the bioavailability regulations under Subpart B—Procedures for Determining the Bioavailability of Drug Products published elsewhere in this issue of the FEDERAL REGISTER. The FDA intends to propose in the near future under the procedures set forth in Subpart C of Part 320 the establishment of a bioequivalence requirement for all of these drug products, which upon examination, are determined to have well-documented, medically significant bioequivalence problems. If a bioequivalence requirement is finally established for a drug product after completion of these procedures, the applicant will be required to submit data in the full or abbreviated NDA to demonstrate that the product meets the bioequivalence requirement.

The Commissioner also advises that FDA's current policy is that, until a bioequivalence requirement is established for a drug product, manufacturers submitting a full or abbreviated NDA for a drug product already identified by FDA as having a known or potential bioequivalence problem will be required to meet the same requirements as previous manufacturers. Thus if previous manufacturers have been required to conduct in vivo studies, new manufacturers will be required to conduct in vivo studies even though there is evidence that a bioequivalence requirement could be established on the basis of an in vitro test. This assures that opportunity for public comment will be provided before an in vitro test is substituted for an existing in vivo test to demonstrate bioequivalence, and that competing firms are treated fairly and equally by the agency. The Commissioner advises that, pursuant to the agency's policy of minimizing human studies, FDA will give priority to the establishment of bioequivalence requirements to those products for which an in vitro test is available.

DEFINITIONS

14. One comment objected to the definition of "drug product" proposed in § 320.1(b). The comment stated the definition should connote an item that is capable of being introduced into interstate commerce and should embrace the active drug ingredient, the labeling, and the final package in which the product is distributed, and not merely the product's dosage form. The comment recommended that "drug product" be defined as "a dosage form defined by the USP monograph in a suitable protective container with labeling that includes directions for use and storage."

The Commissioner does not agree that the term "drug product" should be defined, for the purposes of the bioavailability and bioequivalence regulations, to include the container and labeling. The purpose of defining the term "drug product" is to differentiate that term from the term "drug", i.e., the active drug ingredient. The Commissioner does not believe that the suggested change adds clarity to the definition. On the contrary, he believes that inclusion of the container and labeling in the definition of drug product might mislead persons into believing that a bioequivalence requirement would have to specify the type of container and labeling. The purpose of the bioequivalence regulations is to assure that pharmaceutical equivalents or pharmaceutical alternatives have equivalent bioavailability. The container and labeling have no bearing on this purpose. While a container may affect the stability of a drug product, a product whose strength or purity has deteriorated over time is no longer a pharmaceutical equivalent or a pharmaceutical alternative.

15. One comment concerning the definition of the term "pharmaceutical al-

ternatives" proposed in § 320.1(d) stated that this implies that two different salts may have the same effect, but whereas the rate of deposit in situ may be different, this difference is not an effect of bioavailability.

While the comment is not clear, the Commissioner reiterates that certain pharmaceutical alternatives, as defined in proposed § 320.1(d), should be bioequivalent because their therapeutic effect is based on the same therapeutic moiety and they are labeled to be used interchangeably, e.g., theophylline and aminophylline (theophylline ethylenediamine). On the other hand, other pharmaceutical alternatives, e.g., erythromycin estolate and erythromycin stearate, are not labeled to be used interchangeably and need not be bioequivalent. The Commissioner will propose to establish a bioequivalence requirement for pharmaceutical alternatives only if the labeling indicates that they are intended to be used interchangeably. If pharmaceutical alternatives are not intended to be used interchangeably, the labeling should note differences in pharmacokinetic properties affecting metabolism and tissue distribution, toxicity, and adverse reactions.

16. Two comments recommended that the definition of the term "bioequivalent drug products" proposed in § 320.1(e) be modified to read: " 'Bioequivalent drug products' means pharmaceutical equivalents or pharmaceutical alternatives that have comparable location parameters, e.g., means, medians, etc., with respect to rate and extent of absorption to the reference material, provided that the bioavailability test shall be sufficiently sensitive to discriminate between specified differenees in formulations. A drug product may be equivalent to the reference material in the extent of absorption, but not in its rate of absorption and yet may be considered to be bioequivalent because such differences in rate of absorption may be intentional or are not essential to the attainment of effective body drug concentration on chronic usage." Another comment recommended that confidence intervals should be used to interpret bioequivalence data. The comment stated that the use of confidence intervals would remove the decision on bioequivalence from the statistician, who should not make therapeutic decisions, to its rightful place with the investigating clinician. For example, in a comparative bioavailability trial of a new formulation (B) against a standard formulation (A) of a drug, analysis may indicate that the total urinary excretion of (B) is (with 95 percent confidence) 91.8 to 108.2 percent of the urinary excretion of (A). The investigator can then decide whether this 8.2-percent variation is, or is not, sufficiently small to consider the two preparations therapeutically equivalent.

The Commissioner believes that a determination that two or more pharmaceutical equivalents or pharmaceutical alternatives are bioequivalent drug products should consider not only the statistical significance of numerical values, e.g., means, medians, etc., but also inter- and intra-subject variability, product reproducibility and variability, and the medical significance of differences in bioavailability. For certain drug products, greater variance in bioavailability can be tolerated because of the intended therapeutic use or because the products do not require careful patient titration. In addition, variation in bioavailability must be allowed because the reference material used as a standard for bioequivalence testing will, in most cases, be from a batch of the product produced by the original NDA holder and this reference material, in itself, is not an absolute bioequivalence standard.

As suggested in the first comments, the Commissioner has revised the second sentence in the definition of "bioequivalent drug products" to include a statement that some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic usage, or are medically insignificant for the particular drug product studied. The Commissioner believes that this statement serves to clarify when differences in bioavailability may be tolerated.

The Commissioner, in response to the second comment regarding the use of confidence intervals, has revised the definition of bioequivalent drug products in § 320.1(e) by deleting the word "statistically" because this word incorrectly implies that the statistical significance of numerical values is the sole basis upon which bioequivalence is determined.

Acceptability of In Vitro Data as Evidence of Bioequivalence

17. Two comments stated that in vivo bioequivalence testing should be required, where methodology permits, for all prescription drug products subject to the new drug provisions of the act that have not been studied in clinical trials. Another comment questioned the preamble statement that, for many drug products, in vivo bioavailability testing would involve human risk and would be a waste of human resources with little benefit to the public health. This comment said that a statement should also be made that not testing all drug products could conceivably result in greater harm and risk if ineffectively compounded drug products are allowed on the market.

The Commissioner is of the opinion that, ordinarily, in vivo bioequivalence testing in humans should be limited to those drug products determined to have a medically significant bioequivalence problem. He believes that it is neither feasible nor in the interest of public health to require in vivo testing in humans for all drug products. To conduct in vivo studies to assure the bioequivalence of all marketed drug products, an enormous number of human subjects and clinical investigators would be needed. In addition, the administration of drugs to research subjects is never without some risk or discomfort to the subject. Therefore, in vivo bioequivalence studies are justifiable only where the benefits of the studies outweigh the risks. Furthermore, the Commissioner believes that, for many drug products, the use of a currently available in vitro test comparing the product to a reference material of known bioavailability is adequate to assure the bioequivalence of different brands of the same drug products as well as batch-to-batch uniformity.

18. Several comments objected to proposed § 320.1(f)(1)(i) allowing for the use of an in vitro test, usually a dissolution rate test not correlated with in vivo data, as a method for establishing bioequivalence. These comments stated that a bioequivalence requirement can only be met by an in vivo standard or by specifically showing that the in vitro standard correlates with in vivo data. Unless an in vitro test presents a valid predictive standard for the in vivo bioavailability of a drug product, it should not be used as a standard of bioequivalence. One comment urged that only in vivo testing be used to determine the bioequivalence of drug products unless and until carefully evaluated and validated in vitro methods, unequivocally capable of correlating with bioanalytical findings, are available and published for review by competent scientists.

The Commissioner reiterates his opinion that it is neither feasible nor in the public interest to require in vivo studies in humans for the majority of drug products identified as having a bioequivalence problem. He believes that, ordinarily, in vivo bioequivalence studies should be limited to those drug products for which there is well-documented evidence of therapeutic failure or bioinequivalence in different brands of a drug product that exhibits a narrow therapeutic/toxicity ratio or has an effective concentration in the blood that is in close proximity to the toxic concentration in the blood, and safe and effective use of the drug product requires careful dosage titration and patient monitoring.

The Commissioner believes that a bioequivalence requirement for the majority of drug products should be an in vitro test in which the drug product is compared to a reference material. Preferably, the in vitro test should be an in vitro bioequivalence standard, i.e., an in vitro test that has been correlated with human in vivo data. If an in vitro bioequivalence standard does not exist, however, the Commissioner believes that a solution to a bioequivalence problem is to require an FDA-specified in vitro test not correlated with human in vivo data. Based on current technology, the Commissioner anticipates that, in most instances, the in vitro test will be a dissolution test. Section 320.53 of the final regulations provides for such an in vitro test. The Commissioner advises that a drug product will not be approved for marketing solely on the basis of dissolution rates. A dissolution test, however, may constitute a proper element in reaching the

decision to approve an NDA or supplemental application for a drug product with a bioequivalence problem.

19. One comment stated that, although dissolution rates should be standard analytical procedures, they should not be used as a means of approving a drug product for marketing.

The FDA's experience shows that poor bioavailability is associated with poor dissolution. Where the FDA has performed both blood level studies and dissolution studies on the same lots of different brands of a drug product, test results show that, if there is a significant difference in blood levels, there is also a significant difference in dissolution rates. The FDA, however, is unaware of any instance where noncontrolled release drug products with high dissolution rates were shown not to be bioavailable when tested in vivo.

In most instances, the reference material used in a bioequivalence study will be a drug product that is the subject of an approved NDA. The Commissioner is concerned that the validity of a dissolution rate test will be questioned if the reference material has a low dissolution rate or fails to achieve its full dissolution potential. In proposing a bioequivalence requirement involving an in vitro test not correlated with human in vivo data, the Commissioner will invite comments regarding the adequacy of the test to demonstrate product comparability. The FDA is studying the dissolution rates of a number of multiple source drugs to obtain basic data to support a bioequivalence requirement involving a dissolution test for these products.

20. One comment proposes deleting both the in vitro dissolution testing as an indication of in vivo bioavailability and, in most instances, in vivo studies in humans and replacing both with in vivo animal studies.

The Commissioner agrees that in vivo animal studies may be suitable for demonstrating bioequivalence. To date, however, the FDA has seen little outside data correlating in vivo animal data on the different brands of a drug product or on different batches of the same brand. The FDA is now conducting these studies on some drug products and expects to conduct studies on additional drug products in the future. Information from these studies will provide first hand information as to the extent that animal studies may be able to substitute for human studies where in vivo testing is required. Therefore, until that time, the Commissioner believes that animal studies should be limited to those instances where an in vitro test is not suitable or in vivo testing in humans is impractical or not feasible. Section 320.53 of the final regulations provides for in vivo animal studies in a bioequivalence requirement.

21. The Commissioner also concludes that it is inappropriate to include in the definition of the term "bioequivalence requirement," the types of bioequivalence requirements that may be established. Therefore, in the final regulations he has limited § 320.1(f) to a definition of the term "bioequivalence requirement." He has deleted the information in proposed § 320.1(f)(1) and (2) regarding the types of bioequivalence requirements, and has included this information in new § 320.53.

PROCEDURES FOR ESTABLISHING OR AMENDING A BIOEQUIVALENCE REQUIREMENT

22. One comment proposed deletion of the phrase "or may not be" from proposed § 320.3(a) (now § 320.51(a)(2)). The comment explained that it is a contradiction in terms to impose bioequivalence requirements on products when the Commissioner does not know them to be ordinarily lacking in bioequivalence. Furthermore, if a lack of bioequivalence cannot be established by available scientific techniques, it is doubtful at best that a meaningful bioequivalence requirement could be established. The comment added that, if a bioequivalence requirement is not in fact necessary to assure that a drug is safe and effective for use under the conditions prescribed, recommended, or suggested in its labeling, then it cannot be required under the statute.

The Commissioner agrees in part with this comment; however, he does not agree that the phrase "or may not be" should be deleted. He advises that a bioequivalence requirement will not be established for a particular drug product unless there is well-documented evidence that different brands of the same drug product present a high potential for not being bioequivalent or are not bioequivalent. The Commissioner recognizes, however, that there may be instances where there is well-documented evidence of a bioequivalence problem with several drug products in a class of drug products, e.g., the thiazides, but this evidence does not include data for all of the drug products in the class. The Commissioner is of the opinion that, on the basis of this evidence, protection of the public health requires that he establish a bioequivalence requirement for all of the drug products in the class, and not only for the particular drug products in the class for which there is well-documented evidence of a bioequivalence problem. Proposed § 320.3(b)(7) stated that one of the factors to be considered in determining whether a bioequivalence requirement should be established is evidence that pharmaceutical alternatives or pharmaceutical equivalents are members of a class of drug products that have close structural similarity and physicochemical or pharmacokinetic properties and evidence that other drug products in this same class are not bioequivalent drug products; this has now been merged with proposed § 320.3(a) in new § 320.51(a). The Commissioner advises that the intent of the phrase "or may not be" in proposed § 320.3(a) is to reflect the factor in proposed § 320.3(b). Section 320.51(a) of the final regulations states that a bioequivalence requirement may be established if the Commissioner determines that drug products may not be bioequivalent drug products based on the criteria set forth in § 320.52 or because they are members of a class of drug products and have close structural similarity and similar physicochemical or pharmacokinetic properties to other drug products in the same class that the Commissioner finds proposed § 320.3(a) is to reflect the factor

23. One comment stated that the petition procedures for establishing a bioequivalence requirement in proposed § 320.3(c) would shift to manufacturers FDA's reponsibility for monitoring the safety and effectiveness of other manufacturers' "me-too" products. The comment added that FDA should not establish procedures that would permit the marketing of untested products and that would rely upon manufacturers' testing of competitors' products to detect effectiveness problems.

The Commissioner believes that this comment incorrectly assumes that once the regulations are finalized FDA will take a passive role and wait for manufacturers to submit data on their competitors' products before taking action. This is not the case. The FDA will continue to conduct studies to identify bioequivalence problems with multiple source drug products. The FDA will itself propose to establish a bioequivalence requirement for a drug product if the data needed to establish this requirement are known to the agency. While FDA does not expect manufacturers to submit information on the deficiencies of competing products, it is naive to believe that many manufacturers do not routinely test their competitors' products. In the past manufacturers have submitted data to FDA showing that there are bioequivalence problems with their competitors' products and requested regulatory action. The petition procedure does not transfer to anyone FDA's responsibility to assure the safety, effectiveness, and quality of drug products. The purpose of the procedure is to provide an orderly process for any person, including manufacturers who desire to do so, to submit evidence of a bioequivalence problem to FDA. This procedure will assure, however, that such evidence is public and scientifically valid and that the petition is not simply an attempt to make it harder for competitors to market products.

24. One comment proposed that the following new sentence be inserted between the first and second sentence of proposed § 320.3(c): "A proposal to establish a bioequivalence requirement initiated by the Commissioner of Food and Drugs shall contain the same information required by this section to be included in citizen petitions to establish such a requirement." The comment argued that the Commissioner should subject himself to no less substantial requirements than those imposed on private parties.

The Commissioner agrees that if he proposes to establish a bioequivalence requirement the proposal must contain well-documented evidence to support the proposal. If the Commissioner proposes to establish a bioequivalence requirement, the supporting data will be placed on public display in the office of the Hearing Clerk, Food and Drug Administration, and referred to in the proposal published in the FEDERAL REGISTER for public comment. The Commissioner is

amending § 320.51(c) of the final regulations to clarify this issue.

25. One comment stated that the person petitioning for a bioequivalence requirement having justified the bioequivalence requirement under proposed § 320.3(c)(1) should not be required to provide a proposed in vitro or in vivo test. The comment explained that if a bioequivalence problem is shown to exist, the drug product should be added to the list of drug products needing in vivo or in vitro testing and the same procedures followed as with drug products already listed.

The Commissioner believes that, in the majority of cases, if there is well-documented evidence of a bioequivalence problem, the petitioner will be able to propose an in vitro or in vivo test for determining bioequivalence. The intent of the regulations is to require a petitioner to include in his petition any in vitro or in vivo test he proposes to be used in a bioequivalence requirement. The Commissioner advises, however, that he will not deny a petition solely because it does not contain a proposed in vitro or in vivo test. The Commissioner is modifying the final regulations in § 320.54(b) to state that the petitioner is requested to, but is not required to, include in the petition a description of any in vitro or in vivo test he proposes to be used in a bioequivalence requirement.

26. One comment stated that proposed § 320.3(n) would allow FDA to amend a bioequivalence requirement without revealing the reasons for this requirement. The comment explained that this situation can arise if a revision of a bioequivalence requirement is based on confidential information obtained from one drug company. The comment added that, if a new standard based on confidential information is imposed, it is not possible to know whether an arbitrary standard is being required or whether the standard is justified but based on confidential information. The comment recommended that FDA state when the standard is based on confidential data.

Section 320.51(d) of the final regulations provides that the Commissioner, on his own initiative or in response to a petition by an interested person, may amend a bioequivalence requirement. An amendment will be made with the same criteria and procedural steps that are to be used in establishing a bioequivalence requirement initially. Data submitted in a petition or otherwise available to FDA to support the amendment will be made part of the administrative record. If the amendment proposes a new or revised method based on data in an approved NDA or data voluntarily submitted to FDA and shown to be exempt from public disclosure, the administrative record will include a summary of the data and indicate that the new or revised method is based on data in an approved NDA or on confidential data voluntarily submitted to FDA.

EVIDENCE TO ESTABLISH A BIOEQUIVALENCE REQUIREMENT

27. One comment stated that the proposal is unclear whether the factors listed in proposed § 320.3(b) (now § 320.52) are those to be considered in deciding whether to initiate a proceeding to establish a bioequivalence requirement as well as being the factors that will control the outcome of such a proceeding. The comment proposed that the phrase "which, if demonstrated to be reliable and persuasive, establishes" be inserted prior to the phrase "that such drug products" in proposed § 320.3(b) (1), (2), and (3), and prior to the word "that" appearing in the first lines of proposed § 320.3(b) (4), (5), (6), and (7).

The Commissioner agrees in principle with this comment and advises that the factors listed in proposed § 320.3(b) are to be considered both in deciding whether to propose establishing a bioequivalence requirement and in determining whether a proposed requirement be finalized. In response to the comment, the Commissioner is revising the final regulations in § 320.52 to state that the factors listed, when supported by well-documented evidence, will be considered by the Commissioner to identify specific pharmaceutical equivalents and pharmaceutical alternatives that are not or may not be bioequivalent drug products and to determine whether to propose or promulgate a regulation to establish a bioequivalence requirement for these products.

28. One comment stated that the Commissioner should specify what factors, other than those proposed in § 320.3(b), are referred to in the statement that the "following factors, among others," will be taken into account in a bioequivalence proceeding. The comment stated that it is necessary that all the factors to be considered be spelled out in advance, in order that affected parties may meet the alleged theoretical and factual justification for a proposal that a bioequivalence requirement is necessary for a drug product.

The Commissioner disagrees with this comment. The FDA has attempted to identify prospectively all factors known at this time that would require the establishment of a bioequivalence requirement. These factors reflect the current state of the art and available technology. As with all new regulations relating to an evolving science, the Commissioner reserves the right to consider other factors that may indicate the need to establish a bioequivalence requirement. The Commissioner advises, however, that in establishing a bioequivalence requirement FDA will identify all of the factors considered in determining that a bioequivalence problem exists. Interested persons will have ample opportunity to comment on the scientific merits of these factors before issuance of a final regulation establishing a bioequivalence requirement.

29. One comment stated that proposed § 320.3(b)(1) stipulates that evidence from controlled observations or well-controlled studies in patients that pharmaceutical equivalents or pharmaceutical alternatives intended to be used interchangeably for the same therapeutic effect do not give comparable therapeutic effects will be considered in determining whether to establish a bioequivalence requirement. The comment explained that it would also appear that a lack of well-controlled studies, coupled with a reasonable amount of anecdotal evidence indicating therapeutic failure, should necessitate a direct demonstration of bioavailability. Otherwise, the burden lies not with the new producer of a drug product to demonstrate that his product has comparable bioavailability with those products preceding it on the market, but rather with others to demonstrate that in fact a significant therapeutic risk may exist due to the bioavailability of the product of the new producer.

The Commissioner concludes that a bioequivalence requirement should be established only if there is well-documented evidence that an actual or potential bioequivalence problem exists. Anecdotal evidence is not well-documented evidence. The Commissioner will not establish a bioequivalence requirement on anecdotal evidence alone. In paragraph 7, the Commissioner states his opinion that there are sound reasons for assuming the bioequivalence of pharmaceutical equivalents or pharmaceutical alternatives (based both on data showing the absence of a problem and on the reasonable allocation of scarce technical and human resources), and this assumption is not to be set aside on mere anecdotal contentions.

The Commissioner does not agree that failure to establish a bioequivalence requirement on the basis of anecdotal evidence alters the burden on competing manufacturers, on physicians, consumers, or FDA itself to show that a bioequivalence problem exists with the product of a new producer. The procedures in the final regulations are intended to establish criteria for identifying significant bioequivalence problems that justify additional in vitro and/or in vivo testing to assure that different brands of the same drug product meet the same standards. These procedures provide a means for any person to submit well-documented evidence to support the establishment of a bioequivalence requirement.

30. One comment regarding proposed § 320.3(b)(3) (now § 320.52(c)) stated that an active drug ingredient, not a drug product, has a "therapeutic ratio." The comment added that the inherent pharmacology of the active drug ingredient would determine the therapeutic ratio regardless of the method or rate of delivery to the blood.

The Commissioner does not agree that the therapeutic ratio is a function of the

active drug ingredient and not of the drug product. The therapeutic ratio of an active drug ingredient is not independent from its dosage form. For example, the route of administration affects drug absorption and metabolism and thereby affects the therapeutic ratio.

31. One comment stated that proposed § 320.3(b)(3) does not include the parameters, e.g., the median effective dose (ED_{50}), to be used in determining the therapeutic ratio and, accordingly, the "2-fold difference" guideline should be deleted since it is inherently vague. Another comment stated that the "2-fold difference" guideline seems somewhat arbitrary. This comment added that such a decision would more properly be made for each individual compound, based upon its pharmacology, the nature and severity of the toxic responses, and its pharmacokinetics, especially the rate of elimination and the volumes of distribution. Furthermore, it would be more appropriate to establish a bioequivalence requirement based on therapeutic ratio standards for a group of drug products using those factors that control the biological response to a given dose of a drug product.

The intent of § 320.52(c) is to establish criteria for identifying drug products that require careful dosage titration and patient monitoring for safe and effective use. A bioequivalence problem in these drug products could present a serious health hazard. One method of making such a determination is based on the therapeutic ratio of the drug products. In classical pharmacology the term "therapeutic ratio" is defined as the ratio of the median lethal dose (LD_{50}) to the median effective dose (ED_{50}). See Goodman and Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., p. 27, Macmillan Publishing Co., Inc., New York, 1975. A copy of this reference has been placed on file in the office of the Hearing Clerk, Food and Drug Administration. The therapeutic ratio as defined in classical pharmacology is based partly on the median lethal dose and thus such a determination is usually done in animal studies. For this reason, the therapeutic ratio is rarely used in clinical pharmacology and biopharmaceutics to identify drug products that require careful dosage titration and patient monitoring. This determination is usually made by biopharmaceutical scientists by comparing the minimum effective concentration and minimum toxic concentration in the blood achieved in a multiple dose steady state study. The Commissioner concludes that either the therapeutic ratio of a drug product or a comparison of the minimum effective concentration and the minimum toxic concentration can be used to identify drug products that require careful dosage titration and patient monitoring.

The Commissioner does not agree that the 2-fold difference guideline is arbitrary. He believes that this guideline is generally accepted by the medical community as being adequate to identify drug products that require dosage titration and careful patient monitoring. He emphasizes that this is a guideline that must be applied to an individual drug product on the basis of the product's pharmacology and usage.

The Commissioner is revising the final regulations to specify the parameters to be used in determining the therapeutic ratio and to provide for the comparison of minimum effective concentration and minimum toxic concentration to identify drug products requiring dosage titration and careful patient monitoring.

32. One comment stated that proposed § 320.3(b)(4) (now § 320.52(d)), as written, would not require the establishment of a bioequivalence requirement if a bioequivalence problem could result in a less than serious adverse effect in a serious condition or a serious adverse effect in a less than serious condition. Another comment stated that proposed § 320.3(b)(4) seems to qualify proposed § 320.3(b)(2). This comment explained that it is possible that FDA would allow bioinequivalent products on the market if the agency judged this inequivalence as not being a serious threat in the treatment or prevention of a serious disease condition. The comment added that proposed § 320.3(b)(4) could negate all the other factors to be considered in determining the need for a bioequivalence requirement, since it would be at the discretion of the Commissioner to decide whether this inequivalence would be clinically meaningful.

The Commissioner advises that the intent of § 320.52(d) is to permit the establishment of a bioequivalence requirement where competent medical determination indicates that a lack of bioequivalence would have serious adverse effects in the treatment or prevention of a serious disease or condition even though the available pharmacokinetic or physicochemical data are less than conclusive. Section 320.52(d) does not exclude the establishment of a bioequivalence requirement when a lack of bioequivalence could have a less than serious adverse effect. If evidence demonstrates a known or potential bioequivalence problem, the Commissioner will propose to establish a bioequivalence requirement regardless of whether a lack of bioequivalence could result in a serious adverse effect. The Commissioner, however, does not intend to establish a bioequivalence requirement solely on a medical determination that a lack of bioequivalence could result in a serious adverse effect in the treatment or prevention of a serious disease or condition. A medical determination that a bioequivalence problem could have a serious adverse effect is, of course, of great concern to FDA and would be given great weight in determining whether to establish a bioequivalence requirement if there is other evidence that there is a potential bioequivalence problem even though this evidence is less than conclusive. All of the factors listed in § 320.52 will be considered together in determining whether to establish a bioequivalence requirement. Finally, the Commissioner reiterates that he does not intend to allow drug products with bioequivalence problems to remain on the market. The Commissioner believes, however, that priority should be given to establishing bioequivalence requirements for those drug products where bioequivalence is critical for their safe and effective use in the treatment or prevention of a serious disease or condition.

33. One comment concerning proposed § 320.3(b)(5)(i) (now § 320.52(e)(1)) stated that, although low solubility of a compound has an important effect on its bioavailability from a product, the statement that the dose far exceeds the solubility in the volume of fluids present in the stomach (taken as 100 milliliters) appears to be somewhat vague. The comment added that one cannot determine what fluid is intended or what provisions will be made for doses intended in pediatric patients. Another problem would be those drugs that are utilized in a large range of strengths. By this criterion, fixed volume would affect the testing of increased doses of the same product differently, or a single strength product for which various dosage regimens are suggested for different indications.

The Commissioner agrees that proposed § 320.3(b)(5)(i) is vague and should be revised. The Commissioner advises that the fluid intended is the gastric fluid normally in the stomach. The volume of gastric fluid normally in the stomach is taken to be 100 milliliters for adults and prorated for infants and children. The Commissioner also advises that if a drug product is marketed in more than one dosage strength in the same dosage form and if the volume of gastric fluid required to dissolve any of the dosage strengths far exceeds the volume of gastric fluids normaly in the stomach, he will consider this factor as applicable to all dosage strengths since multiple amounts of this dosage strength may be used.

Section 320.52(e)(1) of the final regulations reads: "The active drug ingredient has a low solubility in water, e.g., less than 5 milligrams per 1 milliliter, or, if dissolution in the stomach is critical to absorption, the volume of gastric fluids required to dissolve the recommended dose far exceeds the normal volume of gastric fluids in the stomach (taken to be 100 milliliters for adults and prorated for infants and children)."

34. Four comments objected to proposed § 320.3(b)(5)(ii) (now § 320.52(e)(2)) that lists a slow dissolution rate, i.e., less than 50 percent in 30 minutes, as one of the factors used to determine whether a bioequivalence requirement should be established. One comment stated that the condition of this determination, such as pH and apparatus, should be specified. The comment added that this is an unnecessarily rigid requirement, and more flexibility is needed. The other comments stated that the standard for slow dissolution is not meaningful because it fails to take into account the nature of the drug entity and its intended function in the body. Another comment stated that the fact that a drug product has a dissolution

rate of less than 50 percent in 30 minutes is not sufficient reason to believe that this product has a bioequivalence problem.

The Commissioner agrees that for some drug products a dissolution rate of less than 50 percent in 30 minutes does not indicate a bioequivalence problem. He believes, however, that such a slow dissolution rate should be one of the factors, but not the only factor, considered in determining whether to establish a bioequivalence requirement. The FDA's experience is that, generally, drug products shown not to be bioequivalent when tested in vivo have a dissolution rate of less than 50 percent in 30 minutes. The Commissioner believes that this guideline can be used as an effective screen to identify drug products with a potential bioequivalence problem that deserve further study. The Commissioner advises that the decision to establish a bioequivalence requirement on the basis of the dissolution rate would consider the dissolution profile of a drug product that is the subject of a full NDA. The Commissioner also agrees that the conditions for determining dissolution rate, such as pH and apparatus, should be specified. The Commissioner is revising § 320.52(e)(2) of the final regulations to read: "The dissolution rate of one or more such products is slow, e.g., less than 50 percent in 30 minutes when tested using either a general method specified in an official compendium or a paddle method at 50 revolutions per minute in 900 milliliters of distilled or deionized water at 37° C, or differs significantly from that of an appropriate reference material such as an identical drug product that is the subject of an approved full new drug application."

35. One comment suggested that proposed § 320.3(b)(5)(iv) (now § 320.52(e)(4)) be amended to read "Certain polymorphic forms, conforms, solvates, complex, crystal modifications, etc., of the active ingredient are poorly dissolved." Another comment stated that it is improper to discuss the absorption of a polymorph according to the presently held view of gastrointestinal absorption where absorption is from the solution state. This comment stated that it would be better to note that polymorphic forms of the same compound may have different dissolution characteristics and thus affect the bioavailability of products containing different polymorphs.

The Commissioner agrees that proposed § 320.3(b)(5)(iv) should be amended to include other physical structural characteristics that may affect bioavailability. Therefore, he is revising § 320.52(e)(4) of the final regulations to read: "Certain physical structural characteristics of the active drug ingredient, e.g., polymorphic forms, conforms, solvates, complexes, and crystal modifications, dissolve poorly and this poor dissolution may affect absorption."

36. One comment stated that, although the physicochemical factors set forth in proposed § 320.3(b)(5)(i), (ii), and (v) (now § 320.52(e)(1), (2), and (5)) are appropriate for consideration in determining whether a bioequivalence requirement should be established, the examples should be deleted because they offer a potential of being misleading since they are at best mere benchmarks.

The Commissioner believes that, although the specific guidelines in proposed § 320.3(b)(5)(i), (ii), and (v) may not apply to all drug products, they are applicable to most drug products and are accepted by biopharmaceutical scientists. To clarify the intent of the inclusion of these guidelines in these sections, however, he has revised the "i.e." notation before each of these guidelines to "e.g."

37. One comment regarding proposed § 320.3(b)(5)(vi) (now § 320.52(e)(6)) stated that it is well known that many excipients used in the manufacture of drug products can have a profound effect on the disintegration, deaggregation, and dissolution of drug products, and thus potentially affect their bioavailability. These excipients are present in nearly every product on the market and the amount used and the mode of application, as well as the ratio of total excipients to active drug ingredient, can have a significant effect on the products.

The Commissioner believes that proposed § 320.3(b)(5)(vi) appropriately reflects the intent of this comment, i.e., excipients used in the manufacture of a prescription drug product may affect its bioavailability, and, therefore, the use of inactive ingredients should be considered in determining whether a bioequivalence requirement should be established. There is no change in § 320.52(e)(6) of the final regulations.

38. One comment regarding proposed § 320.3(b)(6)(ii) (now § 320.52(f)(2)) stated that, although compounds which show poor absorption would be prime candidates for a close scrutiny with respect to bioequivalence, it appears that bioequivalence for the most part involves relative availability using some standard dose such as a marketed product or an oral solution or suspension, rather than the absolute availability utilizing the area under the plasma curve or urinary excretion profile with an intravenous dose. Without such intravenous data, however, the percent absorbed from an oral solution could not be determined.

The Commissioner agrees with this comment. He is revising § 320.52(f)(2) of the final regulations to read: "The degree of absorption of the active drug ingredient, therapeutic moiety, or its precursor is poor, e.g., less than 50 percent, ordinarily in comparison to an intravenous dose, even when it is administered in pure form, e.g., in solution."

39. One comment regarding proposed § 320.3(b)(6)(iii) (now § 320.52(f)(3)) stated that the existence of rapid metabolism through a high hepatic clearance, or intestinal metabolism, would be viewed therapeutically as poor oral absorption when measured as active drug reaching the general circulation. The existence of a high first-pass effect would not have an effect on the relative bioavailability of various oral doses unless the metabolic step was easily saturated so that nonlinear kinetics would be in effect. This latter situation would mean that the extent of absorption was in fact a function of the rate of absorption. Dose dependent bioavailability would result from rapidly releasing dosage forms or solutions with a reduction in the extent of availability with increasing dosage.

The Commissioner believes that the comment misinterprets the clinical significance of the factor set forth in proposed § 320.3(b)(6)(iii). If the active drug ingredient or therapeutic moiety of two drug products undergoes first-pass metabolism either in the gastrointestinal tract or in the liver, the ingredient or moiety of each of the products may be available to the same extent in the systemic circulation at steady state conditions but may differ significantly in their peak concentrations. This difference in concentrations could alter their therapeutic or toxic effects. Drug products that undergo a rapid first-pass metabolism are of greater clinical concern because large differences in peak concentrations will manifest themselves as a function of rates of metabolism and absorption. Therefore, great emphasis may need to be placed on the rate of absorption of a rapidly metabolized active drug ingredient or therapeutic moiety particularly if blood concentrations are critical for the safe and effective use of the drug product.

The comment also refers to dose dependent kinetics where the rate of absorption affects the extent of absorption and, therefore, bioavailability and bioequivalence. The Commissioner agrees that dose dependent kinetics is a factor that should be considered in determining whether to establish a bioequivalence requirement. Therefore, he is adding a new § 320.52(f)(6) that reads: "The drug product is subject to dose dependent kinetics in or near the therapeutic range and the rate and extent of absorption are important to bioequivalence."

40. One comment relating to proposed § 320.3(b)(7) (now § 320.51(a)(3)) stated that it is inappropriate to define a potential for a bioequivalence problem on the basis that a drug product is a member of a closely related class in which a bioequivalence problem has been identified. The comment explained that within a class of compounds there are both very soluble and very insoluble substances and their potential bioequivalence problems relate to each compound's inherent physicochemical properties and not to its relationship to other similar compounds.

The Commissioner advises that if a bioequivalence requirement is established for a class of drug products, the requirement will apply only to the drug products in the class that have close structural similarity and physicochemical or pharmacokinetic properties similar to the drug product for which there is well-documented evidence of a bioequivalence problem. This concept is included in § 320.51(a)(3) of the final regulations.

REQUIREMENTS FOR BATCH TESTING AND CERTIFICATION BY FDA

41. Three comments objected to § 320.3(e) (now § 320.55) regarding individual batch testing and certification by FDA of drug products for which a bioequivalence requirement is established. The comments stated that the agency does not have the authority to require such testing and certification under the act.

The Commissioner concludes that section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) authorizes FDA to require batch testing and certification of drug products where no more practicable means exists to assure that they are safe and effective for their intended use. Section 505 of the act permits a new drug to be marketed only after an NDA provides for safety and effectiveness, under approved labeling, and with approved methods of manufacture and quality control adequate to assure batch-to-batch consistency in making the product so that the product being marketed is identical to that tested for safety and effectiveness and approved by FDA. The Commissioner's opinion is that batch testing and certification may be required in an NDA as part of the methods to assure the drug product's identity, strength, quality, and purity. Ordinarily batch testing and certification for any manufacturer will not be required after four consecutive batches have been certified. The ability of the firm to make a satisfactory product consistently in four batches will generally assure FDA that the methods of manufacture and quality control are adequate.

REQUIREMENTS FOR MARKETING A DRUG PRODUCT SUBJECT TO A BIOEQUIVALENCE REQUIREMENT

42. One comment objected to proposed § 320.3(f) (now § 320.57). The comment stated that a holder of an approved NDA should not have to conduct in vivo bioavailability tests if his product had been shown to be safe and effective in adequate and well-controlled clinical trials.

The Commissioner concludes that, if a bioequivalence requirement is established, each person marketing a drug product that is subject to the requirement must conduct studies to assure that his product meets the requirement and is equivalent to the reference material. In many cases, the drug product that is the subject of an approved NDA has been reformulated or there have been changes in the manufacturing procedures since the approval of the initial application. The reformulated product has not been studied in clinical trials. The FDA's experience is that bioequivalence problems involve products manufactured by holders of approved NDA's as well as those manufactured by persons who do not hold an approved NDA. In addition, the Commissioner believes that clinical trials are not as sensitive, accurate, or reproducible as other bioequivalence methods and should be used to determine bioequivalence only if these other methods are not available.

43. Two comments stated that proposed § 320.3(g) (now § 320.58(a)) should be withdrawn since it would impose a requirement set forth in proposed § 310.7 (21 CFR 310.7) on drug products subject to an NDA approved before October 10, 1962. The comments added that § 310.7 cannot be finalized because of the order of the United States District Court for the District of Columbia in "Hoffmann-LaRoche, Inc., v. Weinberger" (Civil Action No. 75–0270) filed July 29, 1975.

The Court's order in "Hoffmann-LaRoche, Inc. v. Weinberger" was primarily addressed to proposed § 310.7(a), which would have allowed certain drug products to be marketed without prior submission or approval of a full or abbreviated NDA. Proposed § 310.7(c) would have required that, for any drug product subject to a Drug Efficacy Study Implementation (DESI) notice being marketed for the first time after a bioequivalence requirement was established, an NDA be approved before marketing. Proposed § 310.7(c) would have permitted any drug product subject to a DESI notice being marketed at the time a bioequivalence requirement was established to remain on the market pending review and approval or disapproval of a full or abbreviated NDA or supplemental application. This provision was intended solely as a transitional procedure to bring everyone into compliance with a bioequivalence requirement promptly and effectively. The only effect that the Court's order had on proposed § 310.7(c) was to preclude application of the transition procedures to marketed drug products that were not the subject of an approved full or abbreviated NDA at the time a bioequivalence requirement was established. The FDA is taking regulatory action against all drug products known to the agency that were identified in the preamble to the proposed bioequivalence regulations as having a known or potential bioequivalence problem and that are not the subject of an approved full or abbreviated NDA. Thus the transitional procedures in § 310.7(c) that were affected by the Court's order are no longer necessary for those drug products already identified by FDA as having a known or potential bioequivalence problem. In the future, when a bioequivalence requirement is established for a drug product that is subject to a DESI notice and that has not already been identified by FDA as having a known or potential bioequivalence problem, FDA will immediately act to remove from the market all of these products that are not the subject of an approved full or abbreviated NDA. The FDA no longer intends to follow the transitional procedures provided for in proposed § 310.7(c) and no other transitional procedures will be necessary for marketed, unapproved drug products. As discussed in paragraph 46 below, the Commissioner believes that the Court's order, as amended, permits him to establish transitional procedures for marketed drug products that are the subject of an approved full or abbreviated NDA when a bioequivalence requirement is established for these products. Therefore, he is including such transitional procedures in the final regulations.

Section 320.58(a) of the final regulations provides that if a bioequivalence requirement is established for a drug product subject to an NDA that became effective before October 10, 1962, or for any identical, similar, or related drug product covered by such an NDA under § 310.6 (21 CFR 310.6), marketing of the product may lawfully be continued as follows:

a. Any manufacturer who holds an approved full or abbreviated NDA for the drug product on the effective date of the bioequivalence requirement must submit and obtain approval by FDA of a supplemental application that provides evidence that the drug product meets the bioequivalence requirement. If a supplemental application is submitted within the time frame specified in the regulation establishing the bioequivalence requirement, the manufacturer may continue to market the drug product unless and until the supplemental application is disapproved and approval of the NDA is withdrawn.

b. Any manufacturer who does not hold an approved full or abbreviated NDA for the drug product on the effective date of the bioequivalence requirement shall, before introducing the drug product into interstate commerce, submit and obtain approval by FDA of a full or abbreviated NDA, as applicable, that provides evidence that the drug product meets the bioequivalence requirement.

The requirements for a drug product subject to an NDA that became effective before October 10, 1962, or for any identical, similar, or related drug product covered by such an NDA under § 310.6, and further subject to a bioequivalence requirement parallel the requirements proposed in § 320.3(h) (now § 320.58(b)) for a drug product subject to an NDA that was approved on or after October 10, 1962.

44. Two comments objected to proposed § 320.3(h)(2) (now § 320.58(b)(2)) that would allow the submission of an abbreviated NDA for a new drug product first approved after 1962. The comments stated that full NDA's are applicable to post-1962 new drugs, whether or not a bioequivalence requirement has been established. One of the comments recommended that proposed § 320.3(h)(2) be revised to read: "The manufacturer has submitted and obtained approval from FDA of a new drug application containing evidence that the drug product meets bioequivalence requirements and otherwise meets the requirements of Section 314.1(a)–(e) of this chapter."

The Commissioner advises that proposed § 320.3(h)(2) was not intended to permit the submission of an abbreviated NDA for a new drug product that is identical, similar, or related to a new drug product subject to an NDA that was approved on or after October 10, 1962, i.e., after the effective date of the Kefauver-

Harris Amendments to the act. The FDA has not yet permitted the submission of an abbreviated NDA for these post-1962 drug products. Reference to the submission of an abbreviated NDA was included in proposed § 320.3(h)(2) in anticipation that the submission of an abbreviated NDA for these post-1962 drug products may be allowed in the future. To eliminate possible confusion at this time, however, the Commissioner is revising § 320.58(b)(2) of the final regulations to read: "Any manufacturer who does not hold an approved full new drug application for the drug product on the effective date of the bioequivalence requirement shall, before introducing the drug product into interstate commerce, submit and obtain approval by the Food and Drug Administration of a full new drug application that provides evidence that the drug product meets the bioequivalence requirement."

45. One comment stated that proposed § 320.3(i) (now § 320.58(e)) should be withdrawn. The comment explained that, if a drug product is not subject to the new drug provisions of the act, it is an "old drug", and the FDA does not have the legal authority to require submission of bioequivalence data or submission of reports under § 310.300(b)(1) and (2). The comment suggested revision of proposed § 320.3(i) to provide for the voluntary submission of these data and reports with respect to old drugs.

The FDA is reviewing the entire matter of the scope of the new drug provisions of the act and the voluntary or mandatory submission of special reports for all prescription drug products is part of this review. The Commissioner therefore is revising § 320.58(c) of the final regulations to delete the requirement regarding the submission of reports under § 310.300(b)(1) and (2).

The Commissioner concludes, however, that, if a bioequivalence requirement is established for a prescription drug product that is not subject to the new drug provisions of the act, each manufacturer must record and maintain evidence that the product meets the bioequivalence requirement. Such a drug product that does not meet the bioequivalence requirement would be regarded as misbranded under section 502 of the act. For the reasons set forth in paragraph 5, the Commissioner believes that the law presently permits the adoption of a requirement for the submission of evidence that a drug product meets a bioequivalence requirement directly to FDA. Therefore, § 320.58(c)(1) of the final regulations requires a manufacturer of a drug product not subject to the new drug provisions of the act to record and maintain evidence that the product meets the bioequivalence requirement and, upon written request or notice in the FEDERAL REGISTER, to submit this evidence promptly to FDA.

46. Two comments stated that proposed § 320.3(k) (now § 320.58(e)) would permit new drugs to be marketed without prior approval if the Commissioner, in his discretion, so allows. The comment noted that such actions are prohibited by the decision of the Court in "Hoffmann-LaRoche, Inc., v. Weinberger."

The Commissioner advises that the Court's order of July 29, 1975 in "Hoffmann-LaRoche, Inc., v. Weinberger" was amended on November 3, 1975 to add the following separate final paragraph:

ORDERED that nothing in the foregoing provision of this ORDER shall prevent defendants, upon making and publishing in the FEDERAL REGISTER a determination that prescription new drugs in the following categories are medically necessary, from allowing such drugs to continue to be marketed pending completion of scientific studies required for an evaluation of their safety and effectiveness: (a) Drugs covered by approved new drug applications with respect to which new information causes defendants to initiate proceedings to withdraw approvals of applications pursuant to provisions of 21 U.S.C. 355(e); and (b) drugs not previously declared as new drugs and not covered by effective new drug applications, which, upon the basis of new information, the defendants have classified as new drugs.

The amendment to the Court's order was published in the FEDERAL REGISTER of March 2, 1976 (41 FR 9001).

The Commissioner believes that the amendment to the Court's order permits him to stay disapproval of an NDA or supplemental application pending completion of bioequivalence studies.

The Commissioner is revising § 320.58(e) of the final regulations to clarify the conditions under which he may stay disapproval. Section 320.58(e) sets forth that the Commissioner, in his discretion, may stay disapproval for a particular drug product if he finds that all of the following conditions are met:

a. The drug product was being lawfully marketed on the effective date of the bioequivalence requirement, e.g., if a new drug, it was already the subject to an approved full or abbreviated NDA (see paragraph 43).

b. The drug product is medically necessary, e.g., it is used in the treatment of a serious disease or condition for which no alternative therapy is available.

c. There is not an adequate supply of identical or similar drug products subject to an approved full or abbreviated NDA containing bioequivalence data to fulfill medical needs.

d. The manufacturer submits a full or abbreviated NDA or supplemental application, as applicable, containing an acceptable protocol for the conduct of the bioequivalence studies and completes the necessary studies within the time frame set forth in the bioequivalence requirement.

CONFIDENTIALITY OF DATA TO ESTABLISH A BIOEQUIVALENCE REQUIREMENT

47. One comment recommended that proposed § 320.3(m) (now § 320.59) should be revised to make it clear that FDA will not disclose bioequivalence data that are trade secrets.

Section 320.59 is intended to state that a bioequivalence requirement can be established by FDA on the basis of data and information voluntarily submitted to the agency even if these data and information are not publicly disclosable. This section does not govern the disclosability of the actual data and information; the availability of data and information is governed by Part 4 (21 CFR Part 4). The Commissioner stated in the proposal's preamble that FDA intends to maintain the confidentiality of data and information voluntarily submitted to the agency that are trade secrets under § 4.61 (21 CFR 4.61).

48. Two comments regarding proposed § 320.3(m) (now § 320.59) noted that the pharmaceutical industry invests millions of dollars to develop data that may ultimately lead to an in vitro method or animal model that successfully predicts the bioavailability of a drug product. These comments stated that a novel testing apparatus or a better screening procedure offers a competitive advantage that, if disclosed to the public by FDA, would be in violation of 18 U.S.C. 1905 or 21 U.S.C. 331(j).

The Commissioner does not agree with these comments. The Commissioner believes that, if a bioequivalence requirement is established, analytical methods are necessary for regulatory purposes to permit FDA to assure that all marketed drug products meet this requirement. For many years FDA has routinely made available for public disclosure, and has included in its widely distributed manuals, analytical methods that are contained in petitions and NDA's, and which are needed for regulatory assays of drug products. The U.S.P. publishes official analytical methods. Other methods are frequently published in the scientific literature. Accordingly, methods of this type are not customarily regarded as confidential information. The Commissioner believes that an analytical method to determine if a product meets a bioequivalence requirement is not a quality control procedure per se and exempt from public disclosure under § 314.14(g)(1) (21 CFR 314.14(g)(1)), but, rather, is necessary for regulatory purposes to determine if a drug product is safe and effective and may lawfully be marketed. The Commissioner believes that the failure to make such an analytical method public would deter regulatory activity. Accordingly, the Commissioner concludes that all such methods will be made public except where they serve no regulatory function whatever. The Commissioner is including in § 320.59(c) of the final regulations a statement that a bioequivalence requirement may specify an analytical method contained in a petition or an approved new drug application, or that is based on data and information voluntarily submitted to FDA, unless the method serves no regulatory or compliance purpose and is shown to be exempt from public disclosure under § 4.61.

49. One comment regarding proposed § 320.3(m) stated that the proposal to establish tests and standards based on secret data is so novel and raises such serious questions of consistency with established principles of due process that it requires further explanation and opportunity for comment.

The Commissioner advises that if data and information voluntarily submitted to

FDA are determined to be trade secrets under § 4.61 FDA is precluded from disclosing these data and information. If the data and information identify a bioequivalence problem, however, protection of the public health requires FDA to take regulatory action to remedy the problem. The Commissioner believes it is inconsistent with due process to issue a proposed bioequivalence requirement on the basis of "secret data and information" that interested persons can neither see nor comment upon. Therefore, FDA will release a summary of these data and information (see paragraph 47) at the time a proposed bioequivalence requirement is published in the FEDERAL REGISTER. The Commissioner concludes that the comment's proposal to delay finalizing these regulations for further consideration of the procedural question is inconsistent with the public interest. The Commissioner, however, invites any interested person to submit a petition proposing a change in these regulations to prohibit the disclosure of analytical methods to determine bioequivalence. The Commissioner also requests that Congress reconsider whether any safety and effectiveness data, including bioequivalence data and methodology, should be treated as trade secrets.

OLD DRUG MONOGRAPHS

50. One comment concerning proposed § 320.3(o) (now § 320.60) stated that it is assumed that the yet-to-be-formalized old drug monograph concept will include a bioequivalence requirement for such monographed drug.

The Commissioner advises that, one of the approaches to old drug monographs now under consideration in FDA would provide that, if an old drug monograph is established for a drug product for which a bioequivalence requirement has been established, the monograph will include a requirement for bioequivalence testing.

MARKETING PRODUCTS THAT DO NOT MEET AN IN VITRO STANDARD

51. Several comments regarding proposed § 320.3(p) (now § 320.61) questioned why a manufacturer whose product does not meet an in vitro bioequivalence standard must, in lieu of reformulation to meet the standard, demonstrate that his product is bioavailable by in vivo testing of three consecutive batches of the drug product. The comments noted that one lot testing is apparently satisfactory if the product meets the in vitro bioequivalence standard, while in vivo testing is specific, absolute, and represents the primary standard of bioavailability; therefore, the comments suggested that in vivo testing be required for only one batch.

The Commissioner is of the opinion that in vivo testing of a single batch of a drug product that fails to meet an in vitro bioequivalence standard established through correlation with in vivo data is not sufficient to assure batch-to-batch uniformity. Therefore, if a drug product does not meet an in vitro bioequivalence standard, the manufacturer has the option of either reformulating the product to meet the standard or testing three consecutive batches in vivo to demonstrate bioequivalence and batch-to-batch uniformity. The option for in vivo testing was included in proposed § 320.3(p) because the Commissioner recognizes that, occasionally, a drug product that fails to meet an in vitro bioequivalence standard will nontheless be shown to be bioequivalent when tested in vivo. This is because the in vitro bioequivalence standard is designed to identify and screen out all batches that may not be bioequivalent. In selecting the standard, FDA must, if necessary for protection of the public health, err in favor of a standard that may result in the failing of a few batches that are later shown to be bioequivalent when tested in vivo rather than a standard that may result in the passing of a few batches that are shown not to be bioequivalent when tested in vivo. The Commissioner advises that proposed § 320.3 (1) (now § 320.56) requires that if a bioequivalence requirement specifies an in vitro bioequivalence standard, the manufacturer shall conduct the test on a sample of each batch to assure batch-to-batch uniformity. Thus, one lot testing is not satisfactory if the bioequivalence requirement is an in vitro bioequivalence standard.

Requirements for in vivo testing of a drug product not meeting an in vitro bioequivalence standard proposed in § 320.3 (p) have been revised for clarity and are in § 320.61 of the final regulations.

The Commissioner has carefully considered the environmental effects of the regulations and, because the action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. The Commissioner has also carefully considered the inflation impact of the regulations as required by Executive Order 11821, OMB Circular A-107, and Guidelines issued by the Department of Health, Education, and Welfare, and no major inflation impact has been found. Copies of FDA environmental and inflation impact assessments are on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701(a), 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055 (21 U.S.C. 321(p), 352, 355, 371(a)) and under authority delegated to the Commissioner (21 CFR 5.1) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

1. In Part 314:

a. By adding to § 314.111 new paragraph (a)(8) to read as follows:

§ 314.111 Refusal to approve the application.

(a) * * *

(8) The applicant fails to submit bioavailability or bioequivalence data required under Part 320 of this chapter.

* * * * *

b. By adding to § 314.115 new paragraph (c)(5) to read as follows:

§ 314.115 Withdrawal of approval of an application.

* * * * *

(c) * * *

(5) That the applicant has failed to submit bioavailability or bioequivalence data required under Part 320 of this chapter.

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2. By adding new Part 320 consisting at this time of Subparts A and C to read as follows:

Subpart A—General Provisions

Sec
320.1 Definitions.

Subpart B—[Reserved]

Subpart C—Bioequivalence Requirements

320.50 Purpose.
320.51 Procedures for establishing or amending a bioequivalence requirement.
320.52 Criteria and evidence to establish a bioequivalence requirement.
320.53 Types of bioequivalence requirements.
320.54 Contents of a petition to establish a bioequivalence requirement.
320.55 Requirements for batch testing and certification by the Food and Drug Administration.
320.56 Requirements for in vitro testing of each batch.
320.57 Requirements for the conduct of in vivo bioequivalence testing in humans.
320.58 Requirements for marketing a drug product subject to a bioequivalence requirement.
320.59 Bioequivalence requirements based on data voluntarily submitted.
320.60 Bioequivalence requirements for a drug product subject to an old drug monograph.
320.61 Requirements for in vivo testing of a drug product not meeting an in vitro bioequivalence standard.
320.62 Requirements for maintenance of records of bioequivalence testing

AUTHORITY: Secs. 201(p), 502, 505, 701(a), 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055 (21 U.S.C. 321(p), 352, 355, 371(a)), unless otherwise noted.

Subpart A—General Provisions

§ 320.1 Definitions.

(a) [Reserved]

(b) "Drug product" means a finished dosage form, e.g., tablet, capsule, or solution, that contains the active drug ingredient, generally, but not necessarily, in association with inactive ingredients.

(c) "Pharmaceutical equivalents" means drug products that contain identical amounts of the identical active drug ingredient, i.e., the same sat or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates.

(d) "Pharmaceutical alternatives" means drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same

amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates.

(e) "Bioequivalent drug products" means pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied.

(f) "Bioequivalence requirement" means a requirement imposed by the Food and Drug Administration for in vitro and/or in vivo testing of specified drug products which must be satisfied as a condition of marketing.

Subpart B—[Reserved]

Subpart C—Bioequivalence Requirements

§ 320.50 Purpose.

This subpart establishes criteria and procedures for:

(a) Identifying pharmaceutical equivalents and pharamaceutical alternatives that are intended to be used interchangeably for the same therapeutic effect and that are not bioequivalent drug products; and

(b) Establishing a bioequivalence requirement for these drug products.

§ 320.51 Procedures for establishing or amending a bioequivalence requirement.

(a) The Commissioner of Food and Drugs, on his own initiative or in response to a petition by an interested person, may propose and promulgate a regulation to establish a bioequivalence requirement if he finds there is well-documented evidence that specific pharmaceutical equivalents or pharmaceutical alternatives intended to be used interchangeably for the same therapeutic effect:

(1) Are not bioequivalent drug products; or

(2) May not be bioequivalent drug products based on the criteria set forth in § 320.52; or

(3) May not be bioequivalent drug products because they are members of a class of drug products that have close structural similarity and similar physicochemical or pharmacokinetic properties to other drug products in the same class that the Commissioner finds are not bioequivalent drug products.

(b) Any person submitting a petition to the Commissioner to propose a regulation to establish or amend a bioequivalence requirement shall submit the petition under §§ 2.5 and 2.7 of this chapter, and include in the petition the applicable information set forth in § 320.54.

(c) The Commissioner shall include in a notice of proposed rulemaking to establish a bioequivalence requirement the evidence and criteria set forth in § 320.52 that are to be considered in determining whether to issue the proposal. If the rulemaking is proposed in response to a petition, the Commissioner shall include in the proposal a summary and analysis of the relevant information that was submitted in the petition as well as other available information to support the establishment of a bioequivalence requirement.

(d) The Commissioner, on his own initiative or in response to a petition by an interested person, may propose and promulgate an amendment to a bioequivalence requirement established under this subpart.

§ 320.52 Criteria and evidence to establish a bioequivalence requirement.

The Commissioner shall consider the following factors, when supported by well-documented evidence, to identify specific pharmaceutical equivalents and pharmaceutical alternatives that are not or may not be bioequivalent drug products and to determine whether to propose or promulgate a regulation to establish a bioequivalence requirement for these products:

(a) Evidence from well-controlled clinical trials or controlled observations in patients that such drug products do not give comparable therapeutic effects.

(b) Evidence from well-controlled bioequivalence studies that such products are not bioequivalent drug products.

(c) Evidence that the drug products exhibit a narrow therapeutic ratio, e.g., there is less than a 2-fold difference in median lethal dose (LD_{50}) and median effective dose (ED_{50}) values, or have less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and safe and effective use of the drug products requires careful dosage titration and patient monitoring.

(d) Competent medical determination that a lack of bioequivalence would have a serious adverse effect in the treatment or prevention of a serious disease or condition.

(e) Physicochemical evidence that:

(1) The active drug ingredient has a low solubility in water, e.g., less than 5 milligrams per 1 milliliter, or, if dissolution in the stomach is critical to absorption, the volume of gastric fluids required to dissolve the recommended dose far exceeds the volume of fluids present in the stomach (taken to be 100 milliliters for adults and prorated for infants and children).

(2) The dissolution rate of one or more such products is slow, e.g., less than 50 percent in 30 minutes when tested using either a general method specified in an official compendium or a paddle method at 50 revolutions per minute in 900 milliliters of distilled or deionized water at 37° C, or differs significantly from that of an appropriate reference material such as an identical drug product that is the subject of an approved full new drug application.

(3) The particle size and/or surface area of the active drug ingredient is critical in determining its bioavailability.

(4) Certain physical structural characteristics of the active drug ingredient, e.g., polymorphic forms, conforms, solvates, complexes, and crystal modifications, dissolve poorly and this poor dissolution may affect absorption.

(5) Such drug products have a high ratio of excipients to active ingredients, e.g., greater than 5 to 1.

(6) Specific inactive ingredients, e.g., hydrophilic or hydrophobic excipients and lubricants, either may be required for absorption of the active drug ingredient or therapeutic moiety or, alternatively, if present, may interfere with such absorption.

(f) Pharmacokinetic evidence that:

(1) The active drug ingredient, therapeutic moiety, or its precursor is absorbed in large part in a particular segment of the gastrointestinal tract or is absorbed from a localized site.

(2) The degree of absorption of the active drug ingredient, therapeutic moiety, or its precursor is poor, e.g., less than 50 percent, ordinarily in comparison to an intravenous dose, even when it is administered in pure form, e.g., in solution.

(3) There is rapid metabolism of the therapeutic moiety in the intestinal wall or liver during the process of absorption (first-class metabolism) so the therapeutic effect and/or toxicity of such drug product is determined by the rate as well as the degree of absorption.

(4) The therapeutic moiety is rapidly metabolized or excreted so that rapid dissolution and absorption are required for effectiveness.

(5) The active drug ingredient or therapeutic moiety is unstable in specific portions of the gastrointestinal tract and requires special coatings or formulations, e.g., buffers, enteric coatings, and film coatings, to assure adequate absorption.

(6) The drug product is subject to dose dependent kinetics in or near the therapeutic range, and the rate and extent of absorption are important to bioequivalence.

§ 320.53 Types of bioequivalence requirements.

(a) A bioequivalence requirement may be one or more of the following, as specified by the Food and Drug Administration:

(1) An in vivo test in humans.

(2) An in vivo test in animals other than humans that has been correlated with human in vivo data.

(3) An in vivo test in animals other than humans that has not been correlated with human in vivo data.

(4) An in vitro bioequivalence standard, i.e., an in vitro test that has been

correlated with human in vivo bioavailability data.

(5) A currently available in vitro test (usually a dissolution rate test) that has not been correlated with human in vivo bioavailability data.

(b) In vivo testing in humans shall ordinarily be required if there is well-documented evidence that pharmaceutical equivalents or pharmaceutical alternatives intended to be used interchangeably for the same therapeutic effect meet one of the following conditions:

(1) They do not give comparable therapeutic effects.

(2) They are not bioequivalent drug products.

(3) They exhibit a narrow therapeutic ratio, e.g., there is less than a 2-fold difference in LD_{50} and ED_{50} values, or there is less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentration in the blood, and safe and effective use of the product requires careful dosage titration and patient monitoring.

§ 320.54 Contents of a petition to establish a bioequivalence requirement.

(a) Each person submitting a petition to establish a bioequivalence requirement under this subpart shall include in the petition each of the following three types of information to justify this action:

(1) A statement summarizing the bioequivalence problem.

(2) Well-documented evidence that the drug products for which a bioequivalence requirement should be established are pharmaceutical equivalents or pharmaceutical alternatives that are labeled to be administered at the same dose of the same therapeutic moiety for the same therapeutic effect.

(3) Well-documented evidence and data in the categories listed in this paragraph, as applicable, to support the contention that a documented or potential bioequivalence problem exists.

(i) Well-documented evidence that the subject pharmaceutical equivalents or pharmaceutical alternatives do not give comparable therapeutic effects, together with a citation of supporting well-controlled observations or clinical trials in patients and a summary of their contents.

(ii) Well-documented evidence that the subject pharmaceutical equivalents or pharmaceutical alternatives are not bioequivalent drug products, together with appropriate data and/or citations of supporting well-controlled bioequivalence studies and a summary of their contents.

(iii) Well-documented evidence that the subject pharmaceutical equivalents or pharmaceutical alternatives exhibit a narrow therapeutic ratio, e.g., there is less than a 2-fold difference in LD_{50} or ED_{50} values, or have a less than 2-fold difference in the minimum toxic concentration and minimum effective concentrations in the blood, and safe and effective use of the drug product requires careful dosage titration and patient monitoring.

(iv) Competent medical determination that lack of bioequivalence would have a serious adverse effect in the treatment of a serious disease or condition.

(v) Well-documented evidence that the subject pharmaceutical equivalents or pharmaceutical alternatives, because of the physicochemical and/or pharmacokinetic characteristics set forth in § 320.52 (e) and (f), may not be bioequivalent drug products.

(vi) Well-documented evidence to support a finding that the pharmaceutical equivalents or pharmaceutical alternatives are members of a class of drug products that have close structural similarity and physicochemical or pharmacokinetic properties similar to other drug products that have been specifically shown to lack therapeutic equivalence or bioequivalence.

(b) Each person submitting a petition to establish a bioequivalence requirement under this subpart is requested, but is not required, to include in the petition a description of a proposed bioequivalence test as follows:

(1) A description of any proposed current in vitro test to be used pending the development of a definitive in vitro bioequivalence standard together with the evidence described in paragraph (c) of this section that this current in vitro test is suitable for comparing the subject pharmaceutical equivalents or pharmaceutical alternatives to a reference material.

(2) A description of any proposed in vitro bioequivalence standard, including a citation of in vivo data and other evidence described in paragraph (c) of this section which support the applicability of the proposed in vitro bioequivalence standard.

(3) A description of any proposed in vivo bioequivalence test, including the reference material to be used and other technical specification needed to assure uniform testing of the subject pharmaceutical equivalents or pharmaceutical alternatives together with a citation of supporting evidence described in paragraph (c) of this section and a summary of its contents.

(c) Scientific evidence cited in the petition shall include specific, precise information such as:

(1) The product names, batch numbers, labeling, and the identity of the manufacturer, packer, or distributor of the batches of the subject pharmaceutical equivalents or pharmaceutical alternatives included in the studies on which the evidence is based.

(2) The results of all in vitro physical and chemical tests conducted on the batches of the subject pharmaceutical equivalents or pharmaceutical alternatives to determine whether they meet compendial or other applicable standards of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration rates, and dissolution rates.

(3) The results of any in vitro physicochemical tests conducted on the batches of the subject pharmaceutical equivalents or pharmaceutical alternatives studied other than those specified in the compendial or other applicable standard, e.g., particle size.

(4) The results of any in vivo bioequivalence test or in vitro bioequivalence test conducted on the batches of the subject pharmaceutical equivalents or pharmaceutical alternatives studied. These results shall present a validation of the analytical methodology, including the standard curve used and a description of the method of calculation of results, and a description of the pharmacokinetic model and/or statistical model used in analyzing the data.

(5) A full description of the analytical procedures and equipment used in conducting an in vivo or in vitro test on the subject pharmaceutical equivalents or pharmaceutical alternatives.

(d) Each person submitting a petition to establish a bioequivalence requirement under this subpart shall include in the petition copies of published reports in the scientific literature and unpublished material that support the establishment of a bioequivalence requirement for the subject pharmaceutical equivalents or pharmaceutical alternatives.

(e) Each person submitting a petition to establish a bioequivalence requirement under this subpart shall include in the petition information as to the availability of sufficient samples of the subject pharmaceutical equivalents or pharmaceutical alternatives studied to permit confirmatory testing by the Food and Drug Administration.

§ 320.55 Requirements for batch testing and certification by the Food and Drug Administration.

(a) If the Commissioner determines that individual batch testing by the Food and Drug Administration is necessary to assure that all batches of the same drug product meet an appropriate in vitro test he shall include in the bioequivalence requirement a requirement for manufacturers to submit samples of each batch to the Food and Drug Administration and to withhold distribution of the batch until notified by the Food and Drug Administration that the batch may be introduced into interstate commerce.

(b) The Commissioner will ordinarily terminate a requirement for a manufacturer to submit samples for batch testing on a finding that the manufacturer has produced four consecutive batches that were tested by the Food and Drug Administration and found to meet the bioequivalence requirement, unless the public health requires that batch testing be extended to additional batches.

§ 320.56 Requirements for in vitro testing of each batch.

If a bioequivalence requirement specifies a currently available in vitro test or an in vitro bioequivalence standard comparing the drug product to a reference standard, the manufacturer shall conduct the test on a sample of each batch of the drug product to assure batch-to-batch uniformity.

§ 320.57 Requirements for the conduct of in vivo bioequivalence testing in humans.

(a) If a bioequivalence requirement provides for in vivo testing in humans, a manufacturer shall conduct this testing according to the procedures in § 320.24, using the most accurate, sensitive, and reproducible method available, and using the reference material specified in the bioequivalence requirement.

(b) Clinical trials demonstrating safety and effectiveness shall be used to establish bioequivalence only if other methods are not available.

(c) If a bioequivalence requirement provides for in vivo testing in humans using a method other than clinical trials, a manufacturer shall conduct this testing to assure that his product meets the bioequivalence requirement even though his product is the subject of an approved full new drug application containing clinical evidence of safety and effectiveness.

§ 320.58 Requirements for marketing a drug product subject to a bioequivalence requirement.

(a) If a bioequivalence requirement is established for a drug product subject to a new drug application that became effective before October 10, 1962, or for an identical, related, or similar drug product under § 310.6 of this chapter, the product may lawfully be introduced into interstate commerce as follows:

(1) Any manufacturer who holds an approved full or abbreviated new drug application for the drug product on the date the bioequivalence requirement becomes effective shall submit and obtain approval by the Food and Drug Administration of a supplemental application that provides evidence that the drug product meets the bioequivalence requirement. If a supplemental application is submitted within the time frame specified in the regulation establishing the bioequivalence requirement, the manufacturer may continue to market the drug product unless and until the supplemental application is disapproved and approval of the new drug application is withdrawn.

(2) Any manufacturer who does not hold an approved full or abbreviated new drug application for the drug product on the effective date of the bioequivalence requirement shall, before introducing the drug product into interstate commerce submit and obtain approval by the Food and Drug Administration of a full or abbreviated new drug application, as applicable, that provides evidence that the drug product meets the bioequivalence requirement.

(b) If a bioequivalence requirement is established for a drug product subject to a new drug application that was approved on or after October 10, 1962, the product may lawfully be introduced into interstate commerce as follows:

(1) Any manufacturer who holds an approved full new drug application for the drug product on the effective date of the bioequivalence requirement shall submit and obtain approval by the Food and Drug Administration of a supplemental application that provides evidence that the drug product meets the bioequivalence requirement. If a supplemental application is submitted within the time frame specified in the regulation establishing the bioequivalence requirement, the manufacturer may continue to introduce the drug product into interstate commerce unless and until the supplemental application is disapproved and approval of the new drug application is withdrawn.

(2) Any manufacturer who does not hold an approved full new drug application for the drug product on the effective date of the bioequivalence requirement shall, before introducing the drug product into interstate commerce, submit and obtain approval by the Food and Drug Administration of a full new drug application that provides evidence that the drug product meets the bioequivalence requirement.

(c) If a bioequivalence requirement is established for a drug product that is not subject to the new drug provisions of the act, the product may lawfully be introduced into interstate commerce as follows:

(1) The manufacturer records and maintains evidence that the drug product meets the bioequivalence requirement. Upon written request or notice in the FEDERAL REGISTER, the manufacturer shall promptly submit this evidence to the Food and Drug Administration.

(2) The drug product is manufactured in accordance with current good manufacturing practice, as determined by the requirements in Part 211 of this chapter.

(3) The drug product is labeled in compliance with the act and this chapter.

(d) A manufacturer may introduce into interstate commerce a drug product for which a bioequivalence requirement is established only if he complies with this section. Introduction of the drug product into interstate commerce not in compliance with this section is illegal and subject to regulatory action.

(e) Upon disapproval of a full or abbreviated new drug application or supplemental application, the procedures for disapproval of any new drug application under section 505(d) of the act apply. Introduction of the drug product involved into interstate commerce is illegal unless the Commissioner, in his discretion, determines to stay this disapproval for a particular drug product on a finding that all of the following conditions are met:

(1) The drug product was being lawfully marketed on the effective date of the bioequivalence requirement, i.e., if a new drug, it was already subject to an approved full or abbreviated new drug application.

(2) The drug product is medically necessary, e.g., it is used in treatment of a serious disease or condition for which no alternative therapy is available.

(3) There is not an adequate supply of identical or similar drug products subject to an approved full or abbreviated new drug application containing bioequivalence data to fulfill medical needs.

(4) The manufacturer submits a full or abbreviated new drug application or supplemental application, as applicable, containing an acceptable protocol for the conduct of bioequivalence studies and initiates action to conduct and complete the necessary studies within the time frame set forth in the bioequivalence requirement.

§ 320.59 Bioequivalence requirements based on data voluntarily submitted.

(a) A bioequivalence requirement established under this subpart may specify an analytical method, e.g., a current in vitro test, an in vitro bioequivalence standard, or an in vivo bioequivalence test, that is based on data and information voluntarily submitted to the Food and Drug Administration, even though these data and information are exempt from public disclosure under § 4.61 of this chapter.

(b) A summary of the voluntarily submitted data and information on which the bioequivalence requirement is based, prepared in one of the following two alternative ways, shall be publicly released when the bioequivalence requirement is proposed:

(1) The Food and Drug Administration may at an appropriate time before proposing the bioequivalence requirement require the person who voluntarily submitted the data and information to prepare a summary of these data and information, that will be reviewed and, where appropriate, revised by the agency.

(2) The Food and Drug Administration may prepare its own summary of these data and information.

(c) A bioequivalence requirement may specify an analytical method contained in a petition or approved new drug application, or based on data and information voluntarily submitted to the Food and Drug Administration, unless the method serves no regulatory or compliance purpose and is shown to be exempt from public disclosure under § 4.61 of this chapter.

§ 320.60 Bioequivalence requirements for a drug product subject to an old drug monograph.

If the Commissioner establishes an old drug monograph for a drug product for which a bioequivalence requirement has been established under this subpart, the provisions of this subpart as they relate to that drug product are thereby revoked.

§ 320.61 Requirements for in vivo testing of a drug product not meeting an in vitro bioequivalence standard.

(a) If a drug product fails to meet an in vitro bioequivalence standard established under this subpart and a manufacturer nevertheless wishes to market the product without reformulation, the manufacturer may do so if he demonstrates the bioequivalence of the drug product by in vivo testing in humans of three consecutive batches of the drug product and develops an in vitro test that assures the bioequivalence of his product from batch-to-batch.

(b) The reference material to be used by a manufacturer in conducting in vivo testing in humans under this section shall be a drug product that meets the in vitro bioequivalence standard.

§ 320.62 Requirements for maintenance of records of bioequivalence testing.

All records of in vivo or in vitro tests conducted on any marketed batch of a drug product to assure that the product meets a bioequivalence requirement shall be maintained by the manufacturer for at least 2 years after the expiration date of the batch and submitted to the Food and Drug Administration on request.

Effective date: These regulations shall become effective February 7, 1977.

(Secs. 201(p), 502, 505, 701(a), 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055 (21 U.S.C. 321(p), 352, 355, 371(a)).)

Dated: December 30, 1976.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

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[Docket No. 75N-005]

PART 314—NEW DRUG APPLICATIONS

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

Procedures for Determining the In Vivo Bioavailability of Drug Products

The Food and Drug Administration (FDA) is issuing final regulations defining the term "bioavailability" establishing requirements for the inclusion of bioavailability data in certain new drug applications and supplements, and establishing acceptable procedures for determining the bioavailability of drug products. These regulations are effective July 7, 1977.

In the FEDERAL REGISTER of June 20, 1975 (40 FR 26157), the Commissioner of Food and Drugs proposed regulations to define the term "bioavailability," to set forth the purposes of bioavailability studies, and to establish methods and procedures for determining the bioavailability of drug products. Interested persons were invited to submit comments regarding the proposal on or before August 4, 1975. In response to requests, the Commissioner extended the comment period to September 19, 1975, notice of which was published in the FEDERAL REGISTER of August 15, 1975 (40 FR 34407).

The Commissioner received a total of 34 written comments from individuals, trade and professional associations, pharmaceutical manufacturers, and State and Federal government agencies. Twenty of these made substantive comments on the proposed regulations, 4 comments from individual consumers supported action to assure drug uniformity, and 10 other comments were more closely related to other proposed regulations published in the FEDERAL REGISTER of June 20, 1975 (40 FR 26164), and will be considered along with other comments submitted in response to those other proposed regulations. All of the comments may be seen at the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, between the hours of 9 a.m. and 4 p.m., Monday through Friday.

After reviewing the comments and the proposed regulations, the Commissioner concludes that the proposed regulations should be reorganized. He believes that the bioavailability regulations proposed in § 320.2 are too complex to be contained in only one section of the Code of Federal Regulations. Therefore, in the final regulations he is rearranging and redesignating proposed § 320.2 as §§ 320.21 through 320.31 and placing them in new Subpart B—Procedures for Determining the Bioavailability of Drug Products. This action will assure that the bioavailability regulations are easier to find, read, and understand.

To aid the reader, the following table is provided to show the relationship of the final regulations to those proposed in § 320.2.

Proposed	*Final*
§ 320.2(a)	§ 320.21
§ 320.2(b)	§ 320.24
§ 320.2(c)	§ 320.22
§ 320.2(d) (1), (2), (3), and (4)	§ 320.25
§ 320.2(d)(5)(i)–(vi)	§ 320.26
§ 320.2(d)(5)(vii)	§ 320.28
§ 320.2(d)(6)	§ 320.27
§ 320.2(d)(7)	§ 320.29
§ 320.2(d)(8)	§ 320.30(a)-(b)
§ 320.2(d)(9)	§ 320.23
§ 320.2(e)	§ 320.31
§ 320.2(f)	§ 320.30(c)

The substantive comments were concerned with various specific provisions of the proposed regulations and contained recommendations for changes. These comments and the Commissioner's conclusions concerning them are discussed below.

DEFINITION OF BIOAVAILABILITY

1. One comment stated that the term "therapeutic moiety" in the proposed definition of "bioavailability" should be replaced by "parent drug and/or its metabolites." The comment noted that, in determining bioavailability, one is limited by available methodology and knowledge with the result that, in many cases, there is no assurance that the actual therapeutic moiety is measured. This comment also recommended that the phrase "becomes available to the site of drug action" be deleted since it is overly optimistic to presume that bioavailability data consisting of estimates of parent drug and/or metabolite concentration in body fluids, rate of excretion, or the measurement of an acute pharmacologic effect provides, as a general rule, an estimate of the availability of the therapeutic moiety at the site of drug action.

The Commissioner, while agreeing in principle with the comment regarding the term "therapeutic moiety," believes that the term "active drug ingredient" is more appropriate and better understood than the term "parent drug." The Commissioner does not agree that the term "bioavailability" should refer to "metabolites." Although bioavailability may be determined by measurements of metabolites in body fluids or excretory products, bioavailability per se does not involve absorption of metabolites. He also believes that in some drug products the therapeutic moiety, not the active drug ingredient, is absorbed. Therefore, he concludes that the term "active drug ingredient or therapeutic moiety" shall be substituted for the term "therapeutic moiety" in the definition of "bioavailability" in § 320.1.

The Commissioner agrees that bioavailability data alone do not estimate the availability of the therapeutic moiety at the site of drug action. It is scientifically valid to assume, however, that if an active drug ingredient or therapeutic moiety reaches a reasonable extent of systemic circulation at a reasonable rate, the therapeutic moiety will also become available at the site of drug action, e.g., brain, heart, or kidneys. For this reason, the Commissioner concludes that reference to availability at site of drug action should not be deleted. He also believes that omission of such a reference would incorrectly focus the definition of bioavailability exclusively on absorption of the active drug ingredient or therapeutic moiety from the drug product. Even where such absorption is total, the product may not be bioavailable because an insufficient amount of the active drug ingredient or therapeutic moiety reaches the systemic circulation. In certain instances, e.g., high first-pass metabolism in the liver or rapid renal clearance, the active drug ingredient or therapeutic moiety must be absorbed at a rate sufficient to overcome the metabolic or elimination mechanism and reach the systemic circulation so that the therapeutic moiety will become available at the site of drug action in sufficient amounts to elicit the intended therapeutic effect.

The Commissioner also concludes that it is inappropriate to include in the definition of bioavailability the means by which bioavailability is usually estimated. Therefore, in § 320.1 of the final regulations he is defining bioavailability as "the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action." He is deleting the phrase "usually as estimated by its concentrations in body fluids, rate of excretion, or acute pharmacological effect" from the proposed definition of bioavailability. The measurements usually used in a determination of bioavailability are set forth in § 320.24(a) of the final regulations.

2. Another comment suggested that the definition of bioavailability be restricted to the time course of the administered drug in the systemic circulation. This comment stated that it is important that the time dependency of the event be emphasized because it is critical to the definition and, while urinary excretion and acute pharmacological effects are important methods, they are used under the assumption that they re-

flect, via a linear transformation, the rate and extent of availability to the general circulation. Thus, the concept of bioavailability is understood by most of the pharmaceutical scientific community to mean the rate and extent of absorption from those drug products in which the object of the formulation is to put the active drug ingredient into the systemic circulation. The comment also suggested that the definition be restricted to systemic drug products since bioavailability of products intended for topical or local use is not measured by the rate and extent of absorption from these products into the systemic circulation.

The Commissioner disagrees that bioavailability is determined only by measurement of the concentration of the active drug ingredient or therapeutic moiety in the systemic circulation. He concludes that other methods used for determining bioavailability, e.g., measurements of urinary excretion rates or acute pharmacological effects, are based on valid scientific assumptions that are understood and accepted by the scientific community. He also finds that such a restriction is not practicable in view of available methodology and scientific knowledge.

The Commissioner also disagrees that the definition of bioavailability should be restricted to systemic drug products. The concept of bioavailability applies to all drug products. The Commissioner acknowledges, however, that a requirement for bioavailability studies should not apply to certain drug produots, e.g., topicals for local therapeutic effect. Section 320.22 of the final regulations sets forth the criteria that FDA will use to waive a requirement for the submission of evidence of in vivo bioavailability.

3. A third comment stated that, to avoid ambiguity and confusion, the term bioavailability should be redefined to allow a determination of bioavailability by measurement of a number of physical dimensions. The comment suggested that bioavailability be defined as "the sum of knowledge that allows one quantitatively to define, insofar as is technically feasible, the dynamic interrelations among the following: (a) The time-dependent drug release from a pharmaceutical product, (b) the time-dependent concentrations of drug in various body fluids and tissues, (c) the time-dependent concentrations of drug at the sites of its actions, (d) the time-dependent actions of the drug, (e) the time-dependent rates at which drug leaves the body, by its metabolic conversion to other substances and by the excretion of unaltered drug and its metabolites through various routes."

The Commissioner concludes that the definition suggested in the comment is not practical for regulatory purposes. The concepts set forth in the suggested definition are more properly related to the broad subject of pharmacokinetics and pharmacodynamics, than to the more limited concept of bioavailability.

REQUIREMENTS FOR SUBMISSION OF BIOAVAILABILITY DATA

4. Two comments regarding proposed § 320.2(a) indicated that, although there is great emphasis in the proposed regulations on bioavailability problems derived from active drug ingredients, this same emphasis is not given to the effects that changes in inactive ingredients may have on bioavailability. These comments stated that subtle inclusions or changes of inactive ingredients in a drug product may have a significant effect on bioavailability. Another comment indicated that changes in dyes, flavors, or preservatives are not necessarily good examples of significant changes in product formulations. The comment suggested that better examples of significant changes requiring bioavailability tests are changes in excipients, tablet compression, coatings, vehicles, and particle size. One comment noted that the phrase "significant change in product formulation" in proposed § 320.2(a)(1) is too narrow and vague and suggested the phrase be revised to read "changes beyond the variations provided for in the application with respect to product formulation."

The Commissioner agrees with these comments and concludes that any proposed change in the manufacturing process, including a change in product formulation or dosage strength, beyond the variations provided for in the approved application must first be evaluated and approved by FDA. These requirements are included in § 320.21(b) of the final regulations.

The Commissioner advises that past FDA policy has been to require in vivo bioavailability data (particularly pharmacokinetic data) in a supplemental application proposing a change in the labeling to provide for a new indication for use, a new dosage regimen, or an additional dosage regimen for a special patient population, e.g., infants, if clinical studies are required to support the proposed change in the labeling.

In the final regulations the Commissioner is redesignating proposed § 320.2(a) as § 320.21. He is also expanding § 320.21 to clarify the requirements for the submission of in vivo bioavailability data in a full or abbreviated new drug application (NDA) or supplemental application. Section 320.21 requires that any full or abbreviated NDA, and certain supplemental applications, submitted after July 7, 1977, must include either evidence demonstrating the in vivo bioavailability of the drug product that is the subject of the application or information to permit FDA to waive this requirement. (The conditions justifying waiver are discussed below.) Supplemental applications for which bioavailability data or waiver information is required are those proposing (a) a change in the manufacturing process, including a change in product formulation or dosage strength, beyond the variations provided for in the approved application, or (b) a change in the labeling to provide for a new indication for use, a new dosage regimen, or an additional dosage regimen for a special patient population. Bioavailability data or waiver information are required for a proposed change in the labeling only if clinical studies are required to support the proposed change.

5. One comment suggested that the words "concerning a significant change in product formulation" be added after the words "supplemental application" in proposed § 320.2(a)(2). The suggestion was made in order that the wording of paragraph (a)(2) may be consistent with the wording of paragraph (a)(1).

The wording in proposed § 320.2(a)(2) was intended to be consistent with the wording of proposed § 320.2(a)(1). The inconsistency is eliminated in § 320.21 of the final regulations, but the word "significant" has been deleted as discussed in paragraph 4 above.

6. Two comments recommended that the requirements of proposed § 320.2(a)(1) and (2) regarding the submission of bioavailability data in an original NDA be deleted. The comments stated that the inclusion of such data is unnecessary and may contribute to unwarranted delay in approval of the application. Furthermore, they argued, there is no need to show bioavailability of a drug product subject to an original NDA since the product must by clinical data be proven effective and, therefore, bioavailable.

The Commissioner disagrees with these comments. As discussed in paragraph 1 of the preamble to the proposal of June 20, 1975 (40 FR 26157), bioavailability data are necessary to define the pharmacokinetic profile of the new drug and to evaluate the adequacy of the proposed labeling recommendation regarding dosage and administration. These pharmacokinetic data are also needed to assure that the dosage formulation intended for marketing has the same characteristics as the dosage formulation used in clinical studies to determine safety and effectiveness and that there is batch-to-batch consistency. The inclusion of bioavailability data in the application will assist in evaluating future product reformulations or changes in manufacturing processes. As also noted in the preamble to the proposal, a clinical trial to establish the safety and effectiveness of a drug product is the least accurate, sensitive, and reproducible method for determining bioavailability and is adequate only when other methods are not available.

7. Under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)), FDA may require a holder of an approved full or abbreviated NDA to conduct additional in vivo studies to demonstrate the bioavailability of the drug product that is the subject of the application. The Commissioner therefore is including in § 320.21(f) of the final regulations a requirement for the submission of in vivo bioavailability data if FDA notifies the applicant that there are data demonstrating that (a) the

dosage regimen in the labeling is based on incorrect assumptions or facts regarding the pharmacokinetics of the drug product and following this dosage regimen could potentially result in subtherapeutic or toxic levels, or (b) there is significant intra-batch or batch-to-batch variability, e.g., plus or minus 25 percent, in the bioavailability of the drug product. The Commissioner advises that these requirements represent existing FDA policy under section 505(j) of the act. Notice-and-comment rule making procedures are not a prerequisite to promulgation of § 320.21(f) with these final regulations, because it imposes no regulatory requirements but merely describes the criteria used by FDA in determining when to require an NDA holder to submit evidence demonstrating in vivo bioavailability. Section 505(j) of the act authorizes FDA to require, either by general regulation or by order with respect to a specific NDA, an applicant to make reports with respect to the drug subject to the application. For these reasons, the Commissioner finds it unnecessary to utilize notice-and-comment procedures in adopting § 320.21(f); he does, however, invite comments to determine whether these criteria should be amended, modified or revoked. Interested persons may, on or before March 8, 1977, file with the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, written comments in quintuplicate on § 320.21(f). Comments received will be available for public inspection at the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday. Any changes justified by such comments will be the subject of a further order.

8. The Commissioner, to clarify the intent of § 320.21, has included in § 320.21(g) a statement that the requirements for the submission of evidence demonstrating in vivo bioavailability apply only to a full or abbreviated NDA or supplemental application for a finished dosage formulation.

GENERAL APPROACHES FOR DETERMINING BIOAVAILABILITY

9. One comment suggested that the term "therapeutic moiety" in proposed § 320.2(b)(2)(ii) be replaced by the term "parent drug and/or its metabolites." The comment noted that the acute pharmacologic effect measured may not always be elicited by the therapeutic moiety.

The Commissioner agrees, in principle, with this comment. He concludes, however, that the term "active drug ingredient" is more appropriate than "parent drug." He is revising §§ 320.21 through 320.31 of the final regulations to expand the term "therapeutic moiety" to include the active drug ingredient and metabolites, as appropriate.

10. One comment recommended that proposed § 320.2(b)(2)(ii) be revised to specify that the acute pharmacological effect that forms the basis of a bioavailability study should bear a relationship to the anticipated therapeutic effect of the drug product and not an ancillary side effect. The comment indicated, for example, it would be inappropriate to base a bioavailability evaluation of an antidepressant or other drug affecting the central nervous system on an acute cardiovascular or other peripheral pharmacologic response elicited by the compound.

The Commissioner disagrees with this comment. The purpose of a bioavailability study is to determine the rate and extent of the absorption of the active drug ingredient or therapeutic moiety from a drug product. He concludes that it is scientifically valid to determine bioavailability by a measurement of an acute pharmacological effect that is attributable to the systemic circulation of the active drug ingredient or therapeutic moiety, even though this effect does not bear a direct relationship to the drug product's anticipated therapeutic effect. For example, FDA has contracted for bioavailability studies on chlorpromazine hydrochloride (an antiemetic or antipsychotic agent) that relate absorption of the drug to its pharmacological effect on the eye.

11. One comment regarding proposed § 320.2(b)(2)(iii) stated that, although a well-controlled clinical trial may in the abstract seem a less sensitive means of determining bioavailability, such a trial is the superior means for determining therapeutic effectiveness, which is the intended goal of bioavailability studies in the first place. The comment noted that proposed § 320.2(b) implies that bioavailability studies produce more reliable data than the well-controlled clinical trial for determining therapeutic equivalence among drug formulations and tends to give the bioavailability study greater importance than it deserves. The comment suggested that some statements be put in the regulations to reflect a balanced perspective regarding clinical trials.

The Commissioner agrees that clinical trials are the optimal method for determining the effectiveness of a drug product. It is not, however, the intent of a bioavailability study to demonstrate effectiveness. The purpose of a bioavailability study is to determine the rate and extent of absorption. If a drug product is not bioavailable, it cannot be regarded as effective. However, a determination that a drug product is bioavailable is not in itself a determination of effectiveness. The requirement for evidence of bioavailability is intended to supplement, nor replace, clinical evidence of effectiveness. Although clinical trials do demonstrate the bioavailability of a drug product, such trials are not as accurate, sensitive, or reproducible as other methods, e.g., blood level studies, for obtaining bioavailability data. Therefore, the Commissioner concludes that no revision of the regulations is necessary.

12. One comment stated that it is evident that safety and effectiveness, as established in clinical trials, are direct evidence of whether the product is absorbed. For this reason, it is inappropriate to impose a retroactive requirement for in vivo bioavailability data on NDA holders who have conducted clinical trials to establish safety and effectiveness, except in those instances of significant changes in product formulation.

The Commissioner advises that the bioavailability regulations do not require a current holder of an approved NDA to submit bioavailability data on the drug product that is the subject of the application. To conserve testing resources and to implement the requirements for the submission of bioavailability data in an orderly manner and with logical priorities, the regulations are being applied prospectively to all future NDA's and future supplements to existing NDA's. The Commissioner believes that this approach is justified because clinical trials on drug products subject to existing NDA's create a presumption of bioavailability that should remain unless there is evidence to the contrary.

13. One comment, noting that proposed § 320.2(b)(1) states that bioavailability testing shall be conducted using the most accurate and sensitive approach available, questioned whether a manufacturer will be required to conduct additional bioavailability studies if a more sensitive method becomes available after he completes such studies for his drug product using a less sensitive method.

The Commissioner advises that a manufacturer may be required to conduct additional bioavailability studies if a more sensitive method becomes available and if there is evidence that the method used by the manufacturer is not adequate to demonstrate the bioavailability of the drug product. The Commissioner believes that, in view of limited testing resources, it is impractical and not in the interest of public health to require retesting whenever a more sensitive method becomes available, particularly if this new method is only marginally more sensitive than previous methods.

14. One comment suggested that proposed § 320.2 specify that an isotopically labeled drug product may be used for assay in those cases where a more specific assay method is not available.

The Commissioner does not rule out studies using radioactive or nonradioactive isotopes; however, each such study must be considered on an ad hoc basis. The Commissioner concludes that a bioavailability study using an isotopically labeled drug may be deficient in that such a study involves a nonmarketable form of the drug product. The key to proper bioavailability studies is to use the dosage form intended for commercial distribution. If an isotopically labeled version of the drug product is used, it means that a special form of the active drug ingredient is being used. This version may differ in polymorphic form, particle size, or other physicochemical characteristics from the nonlabeled active drug ingredient. The bioavailability of the isotopically labeled drug product may differ from the nonlabeled drug. Such studies, however, may be approved

if the in vivo performance of the isotopically labeled drug product is fully characterized to assure that it is equivalent to the dosage form intended for commercial distribution. The Commissioner is including in § 320.24(d)(4) of the final regulations specific reference to radioactive and nonradioactive isotopically labeled drug products. The Commissioner concludes that a bioavailability study involving a nonradioactive isotopically labeled drug product need not be conducted under a "Notice of Claimed Investigational Exemption for a New Drug" if the study is otherwise exempt from such a requirment under § 320.31. There is no evidence that the use of a nonradioactive isotope per se presents a hazard to research subjects. The use of a radioactively labeled drug product in a bioavailability study shall be under a "Notice of Claimed Investigational Exemption for a New Drug" submitted under § 312.1. The Commissioner is including this requirement in § 320.31(a)(2) of the final regulations.

CRITERIA FOR WAIVER OF IN VIVO BIOAVAILABILITY DATA

15. One comment stated that proposed § 320.2(c)(2)(i) should be revised by adding the words "or oral" after "intravenous." This revision would permit waiver of evidence of in vivo bioavailability for a drug product in solution for oral use.

The Commissioner does not fully agree with this comment. Any oral dosage form, solution or otherwise, must be formulated and manufactured in such a manner that the active drug ingredient or therapeutic moiety is released from the drug product and becomes bioavailable, i.e., the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation and becomes available at the site of drug action. Although release of the active drug ingredient or therapeutic moiety is not a factor in an oral solution, absorption into the systemic circulation depends upon many factors, including the pKa (the negative logarithm of the ionization constant of a chemical compound) of the active drug ingredient or therapeutic moiety, the pH of the physiological environment, lipid solubility, viscosity of the solution, the presence of certain inactive ingredients, and the stability of the active drug ingredient or therapeutic moiety in the gastrointestinal tract. The fact that an oral drug product is in solution does not guarantee its absorption into the systemic circulation. The Commissioner concludes, however, that the requirement for the submission of in vivo bioavailability data shall be waived if a drug product (a) is an oral solution, elixir, syrup, tincture, or similar other solubilized form, (b) contains an active drug ingredient or therapeutic moiety in the same concentration as a drug product that is the subject of an approved full NDA; and (c) contains no inactive ingredient that is known to significantly affect absorption of the active drug ingredient or therapeutic moiety. Section 320.22(b)(5) of the final regulations permits this waiver if all of these conditions are met.

16. Proposed § 320.2(c)(2)(i) could be interpreted as permitting waiver of the submission of in vivo bioavailability data for any intravenous solution.

The Commissioner advises that this was not the intent of the proposal. Bioavailability data are needed to support dosage recommendations if the intravenous solution contains (a) an active drug ingredient or therapeutic moiety that is not the subject of an approved full NDA or (b) an active drug ingredient or therapeutic moiety that is the subject of an approved full NDA but which has not been approved for use in an intravenous solution in the same solvent and concentration. The Commissioner is clarifying the proposal's intent in the final regulations. Section 320.22(b)(1) permits waiver of the submission of in vivo bioavailability data if the intravenous solution contains an active drug ingredient or therapeutic moiety in the same solvent and concentration as an intravenous solution that is the subject of an approved full NDA.

17. One comment regarding proposed § 320.2(c)(2)(ii) and (iii) stated that the term bioavailability is simply unsuitable when applied to vehicles (e.g., emollients and syrups) and devices. Another comment stated that products such as emollients to the skin or syrups used as flavored placebos are not drugs as defined in section 210(g) of the act (21 U.S.C. 321(g)) or drug products as defined in § 320.1(b) of the proposed procedures for establishing a bioequivalence requirement and the final regulations published elsewhere in this issue of the FEDERAL REGISTER. The comment recommended that these examples be deleted from the proposed regulations.

The Commissioner advises that the intent of proposed § 320.2(c)(2)(ii) and (iii) was to specify kinds of drug products for which evidence of in vivo bioavailability may be waived. The Commissioner disagrees that emollients to the skin or syrups used as flavored placebos are not drugs. Such products may be drugs depending upon their intended use. To clarify the intent of the proposal, the Commissioner is revising the final regulations. Section 320.22(b) permits waiver of the submission of in vivo bioavailability data if the product's bioavailability is self evident or not necessary for the product to achieve any of its intended purposes. This section permits waiver if the product is a topically applied preparation intended for local therapeutic effect. The Commissioner is deleting the reference to devices such as lenses for the eye and surgical sutures. These devices are subject to and will be regulated under the provisions of the Medical Device Amendments of 1976, not the new drug provisions of the act.

18. Four comments regarding proposed § 320.2(c)(3) stated that bioavailability cannot be established or guaranteed by an in vitro test without proper in vivo correlation.

The Commissioner concludes that, under the conditions set forth in § 320.22(d) of the final regulations, bioavailability may be demonstrated by evidence obtained in vitro in lieu of in vivo data. These conditions allow in vitro testing only if (a) the in vitro test has been correlated with in vivo data, (b) the test product is compared to a reference material that has been shown to be bioavailable, or (c) the test product is compared to an identical drug product that is the subject of an approved full or abbreviated NDA. The Commissioner believes that this approach is justified in view of the limited resources available for in vivo testing and is in keeping with the guiding principle that no unnecessary human research should be done.

19. One comment stated that in vitro testing may be adequate to demonstrate the equivalence of a reformulated drug product if the reformulation involves changes in color, flavors, or preservatives.

The Commissioner agrees and the final regulations under § 320.22(d)(4) permit in vitro testing when the proposed reformulated drug product is identical, except for color, flavor, or preservatives, to another drug product made by the same manufacturer, e.g., the same product before reformulation, and if the in vitro test approved by FDA compares the reformulated product to the other drug product and that other product has previously been shown to be bioavailable.

20. One comment noted that proposed § 320.2(c)(3)(ii) requires the use of an in vitro dissolution test. The comment stated that in vitro indicators other than dissolution tests have been used that successfully correlate with in vivo results and recommended that the statement "in vitro dissolution test" be changed to read "in vitro test."

The Commissioner agrees and is amending the final regulations to delete the word "dissolution" wherever it appears in conjunction with a requirement for in vitro testing.

21. The Commissioner concludes that the requirements for the submission of evidence demonstrating the in vivo bioavailability of a solid oral dosage form (other than an enteric coated or controlled release dosage form) of a drug product determined to be effective for at least one indication in a DESI (Drug Efficacy Study Implementation) notice, or identical, related, or similar to such a drug product under § 310.6 (21 CFR 310.6), shall be waived if the drug product is neither one of those identified in the preamble to the proposed bioequivalence regulations as having an actual or potential bioequivalence problem (see proposed procedures for establishing a bioequivalence requirement published in the FEDERAL REGISTER of June 20, 1975 (40 FR 26164)) nor an identical, related or similar drug product. The FDA, in preparing the proposed bioequivalence regulations, reviewed all of the drug products evaluated as effective for at least one indication in a DESI notice and determined that, except for those drug products listed in the preamble, there is at the present time no evidence that these drug products have a known or

potential bioequivalence problem. The Commissioner believes that this approach is justified in view of the limited availability of resources for in vivo testing and is in keeping with the guiding principle that no unnecessary human research be conducted. The Commissioner, on his own initiative, has amended § 320.22(c) of the final regulations to permit such a waiver. Section 320.22(c) specifies those drug products determined to be effective for at least one indication in a DESI notice that have been identified by FDA as having a known or potential bioequivalence problem. Those drug products are the same as those listed in the preamble to the proposed bioequivalence regulations except that drug products not evaluated as effective for at least one indication have been deleted.

The Commissioner advises that, on an ad hoc basis, additional data regarding product specifications or testing may be required for approval of a full or abbreviated NDA for individual drug products if these data are needed to assure proper manufacturing controls or biopharmaceutical quality. These data may include, among others, requirements regarding particle size or in vitro dissolution testing.

The Commissioner also advises that the requirements of Subpart B of Part 320 regarding the submission of bioavailability data for drug products evaluated as effective for at least one indication in a DESI notice, or identical, related, or similar to such products under § 310.6, supersede all requirements for the submission of bioavailability data in prior individual DESI notices. The Commissioner also advises that the procedures for establishing a bioequivalence requirement (see Subpart C of Part 320 published elsewhere in this issue of the FEDERAL REGISTER) will be used to establish requirements for the submission of bioequivalence data for drug products evaluated in the Drug Efficacy Study. When a bioequivalence requirement is established for any of the drug products listed in § 320.22(c), the Commissioner will act to amend this section to delete the drug product.

22. The Commissioner, on his own initiative, is also amending § 320.22(e) of the final regulations to permit FDA, for good cause, to defer or waive a requirement for the submission of evidence of in vivo bioavailability if deferral or waiver is compatible with the protection of the public health. The Commissioner believes that these provisions are necessary to allow FDA to permit the continued marketing of medically important drug products while adequate methodology is being developed or bioavailability studies are being conducted. For example, FDA may defer or waive the requirement for the submission of evidence of in vivo bioavailability when FDA, on the basis of new evidence, requires manufacturers to reformulate their products to delete an inactive ingredient. The FDA may also defer such a requirement if adequate methodology is not available for in vivo testing. The Commissioner believes that such a deferral is necessary to avoid the conduct of an improper study and unwarranted human research. In deferring or waiving such a requirement, FDA will consider whether protection of the public health will best be served by such deferral or waiver or by removal from the market of the drug products until the required data are submitted in a supplemental application.

GUIDELINES FOR THE CONDUCT OF IN VIVO BIOAVAILABILITY STUDIES

23. Two comments suggested that the guidelines for the conduct of in vivo bioavailability studies be revised to indicate that, for systemic drug products, the reference material of choice is the same active drug ingredient or therapeutic moiety administered intravenously in solution.

The Commissioner does not agree that the intravenous administration of a solution of the active drug ingredient or therapeutic moiety is necessarily the reference material of choice in determining the in vivo bioavailability of systemic drug products. Intravenous solutions can be utilized only if there are data available that demonstrate the safety of the intravenous administration of the active drug ingredient or therapeutic moiety, to assure that the intravenous administration is not toxic or does not produce adverse, life-threatening effects. In the absence of information about the performance of the intravenous administration of the drug in humans, such studies should be limited to animals.

REFERENCE MATERIALS

24. Three comments recommended that proposed § 320.2(d)(1)(i) be revised to make clear that the use of an oral solution or suspension as a reference material can give only an index of the relative bioavailability, because a comparison with that form and the pharmacokinetic description derived will always contain the unknown factor of the fraction of the dose absorbed. Moreover, it is quite conceivable that a dosage form could be developed which, by means of surfactant, buffering, or other pharmaceutical techniques, shows better bioavailability than a solution or suspension form of an inherently poorly absorbed drug.

The Commissioner recognizes that only an index of the relative bioavailability can be determined by the comparison of a drug product to an oral solution or suspension of the active drug ingredient or therapeutic moiety. This was the intent of the proposed regulations. Section 320.25(d) of the final regulations, however, provides for a determination of absolute bioavailability where necessary and where data are available to show that the reference material may safely be administered intravenously in humans.

25. Another comment regarding proposed § 320.2(d)(1)(i) stated that the reference material should be a solution of the product or other appropriate dosage form but not a suspension because of the bioavailability variability of the suspension dosage form. This comment stated that in many instances a suspension of a poorly soluble active drug ingredient may be more poorly absorbed than a well-formulated tablet because of the presence of suspending agents which add viscosity, may bind to the ingredient, and, in general, may decrease both the rate and extent of absorption.

The Commissioner has determined that the provision of proposed § 320.2(d)(1)(i) (now § 320.25(d)(1)) allowing for the use of an oral suspension as a reference material is intended to cover those instances where the active drug ingredient or therapeutic moiety was not soluble in a solvent that is generally recognized as safe for human consumption. In such cases, a suspension may be an appropriate reference material provided any suspending agents used in preparing the suspension do not affect the bioavailability of the suspension and are generally recognized as safe for human consumption.

26. One comment questioned the example cited in the last sentence of proposed § 320.2(d)(1)(ii) providing that, in the case of a newly marketed tablet of a drug already marketed for intravenous administration only, the reference material shall ordinarily be not only the currently marketed intravenous solution but also the pure drug substance in an oral solution or suspension. The comment stated that it is difficult to see the benefit of the additional sampling necessary for a three-way study involving an oral solution or suspension of the drug when the optimum reference for bioavailability already exists as the intravenous form, unless the compound or product is such as to raise the suspicion of a problem with the bioavailability of the oral dosage form.

The Commissioner concludes that when a new dosage form of a drug (already marketed in another dosage form) is proposed for marketing, it is necessary to characterize fully the pharmacokinetic profile of the new dosage form to support dosage recommendations. The selection of the reference material depends upon the scientific questions to be answered and the data needed to establish dosage recommendations. He agrees with this comment, however, that in the specific example cited such information can be obtained using the intravenous dosage form of the drug product as the sole reference material and in § 320.25(d) of the final regulations has deleted the example.

27. Two comments stated that proposed § 320.2(d)(1)(ii) does not adequately differentiate formulation changes involving alternate routes of administration from other types of changes. For example, there should be no expectation that the bioavailability of orally, parenterally, and rectally administered drug products will be comparable, and it may be desirable for a dosage form with a different route of administration not to be "comparable" to the marketed drug product. The comment suggested that the last sentence in this section be

modified to state that when a new formulation, a new dosage form, or a new salt or ester of a marketed drug product is to be administered by an alternative route to those of the currently marketed drug product, the purpose of an in vivo bioavailability test is to determine the bioavailability of the proposed dosage form relative to a reference material.

The Commissioner agrees that it may be desirable for different dosage forms of the same active drug ingredient or therapeutic moiety to have different bioavailability profiles and that the purpose of a bioavailability study is to determine the bioavailability of the new dosage form. He concludes, however, that the regulation should clarify that bioavailability data are needed to define the pharmacokinetic profile of the new dosage form to establish dosage recommendations. The selection of the reference material will vary. For example, if the new dosage form is a tablet and the dosage form currently marketed is a suspension, the appropriate reference material would be not only the marketed dosage form but also the active drug ingredient or therapeutic moiety in an oral solution. However, if the new dosage form is a tablet and the dosage form currently marketed is an intravenous solution, the appropriate reference material would be the marketed dosage form. The appropriate reference material will vary depending upon the scientific questions to be answered and the data needed to establish dosage recommendations. The Commissioner is revising § 320.25(e) of the final regulations to state that the purpose of an in vivo bioavailability study involving a drug product that is a new formulation, a new dosage form, or a new salt or ester of an active drug ingredient or therapeutic moiety that has been approved for marketing is (a) to determine the bioavailability of the new formulation, new dosage form, or new salt or ester relative to an appropriate reference material and (b) to define the pharmacokinetic parameters of the new formulation, new dosage form, or new salt or ester to establish dosage recommendations. In such a case, the selection of the reference material(s) depends upon the scientific questions to be answered, the data needed to establish comparability to a currently marketed drug product, and the data needed to establish dosage recommendations.

CONTROLLED RELEASED DRUG PRODUCTS

28. One comment suggested that, for clarification, the words "controlled release" be inserted before the word "claims" at the end of the first sentence in proposed § 320.2(d)(1)(iii). As revised the sentence would read: "For a new drug product for which a controlled release claim is made, the purpose of an in vivo bioavailability test is to determine that the new product meets the controlled release claims made for it."

The Commissioner disagrees with that comment. He concludes that the purposes of an in vivo bioavailability study of a controlled release drug product are to determine: (a) If the drug product meets the controlled release claim made for it, (b) if the bioavailability profile established for the drug product rules out the occurrence of any dose dumping, (c) if the drug product's steady-state performance is equivalent to a currently marketed noncontrolled release or controlled release drug product that contains the same active drug ingredient or therapeutic moiety, and (d) if the drug product's formulation provides consistent pharmacokinetic performance between individual dosage units. He is revising § 320.25(f) of the final regulations to clarify the purpose of a bioavailability study for a controlled release drug product.

COMBINATION DRUG PRODUCTS

29. One comment objected to proposed § 320.2(d)(3) requiring that combination drug products must establish bioavailability by reference to simultaneous administration of the individual active drug ingredients. The comment stated that, if an in vivo-correlated in vitro bioavailability test exists for each component, and the component is established to be bioavailable from the combination in accordance with that test, then consistent with the mandate in other sections of the proposal to limit human testing, there is no good reason to require that bioavailability of each component be established by reference to simultaneous administration of each component, unless reason exists to suspect a probable drug interaction affecting the bioavailability of a component from the combination. Another comment stated that in certain combination products the purpose of the second ingredient may actually be to enhance or inhibit the rate of absorption of the primary ingredient and, therefore, provision for this type of combination should be included in the regulation.

The Commissioner advises that the intent of the regulations is to establish that, generally, the purpose of a bioavailability study involving a combination drug product is to determine if the rate and extent of absorption of each active drug ingredient or therapeutic moiety in the combination drug product is equivalent to the rate and extent of absorption of each active drug ingredient or therapeutic moiety in separate single-ingredient preparations given concurrently. The Commissioner reiterates that the regulations require the submission of in vivo bioavailability data unless the requirement is waived. Section 320.22 of the final regulations permits waiver of this requirement for a number of reasons, including evidence that the product meets an in vitro test that assures bioavailability, i.e., an in vitro test that has been correlated with in vivo data. Thus the requirement for the submission of in vivo data may be waived if the applicant submits evidence that the components of a combination drug product meet an in vitro test that assures that each component is bioavailable.

The Commissioner recognizes that in certain cases a second ingredient in a combination drug product is intended to affect the rate or extent of absorption of the primary active drug ingredient or therapeutic moiety. For example, probenecid may be combined with ampicillin to inhibit the tubular renal secretion of ampicillin and thus increase ampicillin plasma levels. The Commissioner is revising § 320.25(g)(3) of the final regulations to permit a bioavailability study involving a combination drug product to determine the rate and extent of absorption of selected, but not all, active drug ingredients or therapeutic moieties in the combination drug product. The FDA may permit this determination if the pharmacokinetics and interactions of the active drug ingredients or therapeutic moieties in the combination drug product are well known and the therapeutic activity of the combination drug product is generally recognized to reside in only one of the active drug ingredients or therapeutic moieties.

CRITICALLY ILL PATIENTS

30. Two comments questioned proposed § 320.2(d)(4) banning bioability testing using critically ill patients. The comments stated that it is conceivable that products intended for use in a vastly altered physiological setting, such as altered clearance rate, electrolyte imbalance, or hemodynamic changes, could be validly examined only in studies involving critically ill patients suffering from renal, respiratory, or cardiovascular insufficiency. One of these comments added that it is appreciated that the therapeutic support of the patient is paramount and studies in critically ill patients should be allowed only under very special situations where the patient's safety is uncompromised and the scientific goals warrant the study.

The Commissioner stated in the preamble to the proposed regulations that, in the cases cited in the comment, bioavailability studies may be conducted on suitable noncritically ill patients. He believes that studies on critically ill patients are inappropriate and contrary to the best medical interest of such individuals unless there is a potential benefit to the patient. He recognizes that concomitant bioavailability studies can be conducted using critically ill patients to allow for dosage titration and further dosage prediction. These studies offer a direct benefit to the patient because the study results can be used to customize the dosage regimen for the critically ill patient. For example, a bioavailability study with kanamycin in uremic patients would permit dosage adjustments based on renal creatinine clearance and serum creatinine levels. Therefore, the Commissioner is revising § 320.25(a)(3) of the final regulations to state that critically ill patients shall not be included in an in vivo bioavailability study unless the attending physician determines that there is a potential benefit to the patient. Pharmacokinetic studies in critically ill patients with an established formulation for the purpose of determining the effects of a disease mechanism on drug metabolism and drug action are in no way prohibited or hindered by these regulations.

SUBJECT VARIABILITY

31. One comment stated that the procedures used by the majority of investigators to determine bioavailability do not compare the physiological variables of subjects receiving test and reference materials, rather they compare mean values of a measured variable. The comment added that, although these investigators have measured the extent of absorption, they have not measured the rate of absorption in determining the bioavailability of a drug product. The comment stated that, if the proposed regulation is implemented, FDA must insist on a reevaluation of the submitted evidence of bioavailability for all marketed drug products and should not accept evaluations that have compared the average extent of absorption.

The Commissioner agrees that early bioavailability studies did not consider inter- and intra-subject variabilities. In the last 3 years, however, FDA in reviewing bioavailability data has considered subject variabilities. The FDA has always considered both the extent and rate of absorption in approving bioavailability studies. Thus, the data submitted within the last 3 years have been evaluated using the guidelines set forth in the bioavailability regulations. The Commissioner does not believe that failure of the early studies to consider subject variabilities is reason to reevaluate the early bioavailability studies unless there is evidence that the drug products included in such studies have a bioequivalence problem. The procedures that the Commissioner is establishing in Subpart C of Part 320 (see the June 20, 1975 proposed procedures for establishing a bioequivalence requirement and the final regulations published elsewhere in this issue of the FEDERAL REGISTER) are intended to provide a mechanism for reviewing the bioequivalence of marketed drug products and for establishing additional testing requirements for those drug products with bioequivalence problems.

SAMPLING TIME INTERVALS

32. Two comments regarding proposed § 320.2(d)(5) (iii) and (iv) stated that this section requires that sampling time intervals for both the test product and the reference material be similar; however, to obtain competent estimates of the rate and extent of absorption, sampling time intervals occasionally need not be the same. For example, in a study comparing an intravenous solution to a tablet, one may desire to take many blood samples shortly after injection of the intravenous solution whereas, because of the characteristics of absorption from a tablet, only a relatively few blood samples need be taken during the same time period. Clearly, patients should not be subjected to needless sampling of blood. These comments suggested that in proposed § 320.2(d)(5) (iii) and (iv) the language "* * * similar time intervals for both the test product and the reference material. Such samples shall be taken with * * *" be deleted. Another comment stated that the words "similar time intervals" in proposed § 320.2(d)(5) (iii) and (iv) should be changed to "identical time intervals" to assure true equivalence.

The Commissioner concludes from these comments that there is a misunderstanding regarding the intent of proposed § 320.2(d). This section is intended to provide general guidelines for the study of a multitude of drug products each of which could require a unique approach. For this reason, he rejects the comment that samples of body fluids should be collected at identical time intervals; such a requirement would not permit the variability needed in studying different products. To clarify these provisions, the Commissioner is revising § 320.26(c) and (d) of the final regulations to provide general guidelines for selection of sampling times. To allow flexibility in the selection of sampling times, he is deleting the phrase "similar time intervals for both the test poduct and the reference material." By way of example, § 320.26(c) of the final regulations states that, in a study comparing oral dosage forms, the blood sampling times should be identical. In a study comparing an intravenous dosage form and an oral dosage form, the blood sampling times should be those needed to describe both the distribution and elimination phase of the intravenous dosage form, and the absorptive and elimination phase of the oral dosage form. For other drug delivery systems, the sampling times should be based on valid scientific reasons.

33. One comment stated that, to assure some flexibility in the selection of urine sampling times, the phrase "unless some other approach is more appropriate for valid scientific reasons" should be inserted at the end of the last sentence in proposed § 320.2(d)(5)(iv).

The Commissioner agrees and is including the phrase suggested in the comment in § 320.26(d) of the final regulations.

34. Three comments objected, as being somewhat arbitrary, to the requirements in proposed § 320.2(d)(5)(iii) and (v) which stated that a drug product must be followed for three half-lives to study it for bioavailability purposes by plasma assay or acute pharmacological effect. The comments noted that three half-lives may not be sufficient in some cases. The duration of the study must instead be based upon the pharmacokinetics of the compound under discussion and suggested that a more reasonable statement might be to ask that the study be continued for a sufficient period to allow for the achievement of a valid bioavailability comparison between the test and reference material. The comments added that, if three half-lives is nonetheless to be a minimum standard, the appropriate portions of these paragraphs should be changed to read: "the total area under the time curve for a time period for at least three times the half-life or sufficiently longer for accurate determination of the individual terminal half-lives."

The Commissioner believes that the pharmacokinetic profile of most drug products can be determined by measuring the rate and extent of absorption for a period of three half-lives of the active drug ingredient, therapeutic moiety, or its metabolite(s) being measured. For some drug products, measurement must be made for a longer period, e.g., five half-lives, because the profile can be determined only by following the rate and extent of absorption for longer than three half-lives. Measurement for three half-lives is intended as a minimum requirement unless another approach is appropriate for valid scientific reasons. The Commissioner emphasizes the words "at least" in proposed § 320.2(d)(5)(iii) and (v), which read in part: "for a time period at least three times the half-life * * *." The Commissioner rejects the proposed alternative wording of the comment as adding nothing to the current language of § 320.26(c).

35. One comment suggested a revision of proposed § 320.2(d)(5)(iv) by changing the words "and extent of urinary excretion" to "and the total urinary excretion."

The Commissioner does not agree with this comment because "total urinary excretion" implies that the active drug ingredient, therapeutic moiety, or metabolite(s) being measured will be completely eliminated in the urine during the time frame in which urinary excretion is being studied. For many drug products, the pharmacokinetic profile of the drug product may be adequately determined before all of the active drug ingredient, therapeutic moiety, or metabolite(s) being measured is eliminated in the urine.

The Commissioner has revised the term "concentration-time curves" in § 320.26(d) of the final regulations to read "cumulative urinary excretion-time curves" because the concentration of the active drug ingredient, therapeutic moiety, or metabolite in the urine depends upon the fluid intake and renal function, thereby making comparison based on concentration unfeasible. Such concentration varies from subject to subject and from day to day in a crossover study.

DATA CORRELATION

36. One comment suggested that the word "correlation" in proposed § 320.2(d)(5)(vii) be changed to "cannonical correlation and/or partial correlation." The comment stated that the statistical procedures commonly used by investigators do not allow for a simple correlation.

The Commissioner does not accept this comment. The term "correlation" as used in proposed § 320.2(d)(5)(vii) (now § 320.28) is not intended to be applied in a statistical sense, but rather to express the concept of showing a cause-and-effect relationship between variables.

37. One comment objected to the statement in proposed § 320.2(d)(5)(vii) that correlation of bioavailability with acute pharmacological effects or clinical evidence of effectiveness may be required if needed to establish the clinical significance of special claims, e.g., in the case of a controlled release preparation. The comment stated that no reason is given for singling out controlled release preparations and none is apparent. The com-

ment added that for purposes of demonstrating bioavailability, data verifying claims of protracted availability of the active moiety in body fluids in vivo are sufficient.

This section was not intended to single out controlled release dosage forms but to emphasize the need for correlation of pharmacological effects with bioavailability data to support labeling claims. Bioavailability was purposely defined both in terms of rate and extent of absorption, because it can be shown with certain drugs that alterations in rate of absorption may impart significantly differences in pharmacological properties of a drug. In such cases, correlation studies with clinical data may be required for approval of a new dosage form that differs in rate but not extent of absorption. Controlled release preparations were selected as an example because it often can be shown that an increase or decrease in side effects coupled with an increased duration of action is associated with significant differences in the pharmacokinetic profile.

The Commissioner, on his own initiative, is amending § 320.28 of the final regulations to include the word "safety" in the phrase "clinical evidence of effectiveness may be required," because in many instances safety considerations are of prime concern.

SINGLE-DOSE AND MULTIPLE-DOSE STUDIES

38. One comment stated that, with respect to proposed § 320.2(d)(6) (now § 320.27), multiple-dose studies performed in the manner proposed are difficult to execute and do not contain sufficient experimental safeguards to assure that a valid estimate of bioavailability will result. Thus, no recognition is given to the usefulness of terminal plasma disappearance data or to estimates of bioavailability under nonsteady-state conditions. The complexities of multiple-dose comparisons are not readily amenable to detailed guidelines for their implementation. The comment suggested that proposed § 320.2(d)(6)(i)–(v) be deleted and the following be inserted in its place: "(6) In selected circumstances, it may be necesary for the test product and the reference material to be compared after repeated administration. The same considerations as in single-dose studies shall generally apply, (except that the method of administration, e.g., fasting and non-fasting, shall reflect the proposed labeling of the drug product) unless some other approach is more appropriate for valid scientific reasons."

The Commissioner agrees that multiple-dose studies are difficult to execute and that there is an obvious need for subject monitoring in such studies. There are, however, a number of circumstances where such studies are the optimal methods to demonstrate the bioavailability of a drug product. While it is not the intent of the Commissioner to constrain research on new methodology in this area, it is his opinion that some broad guidelines should be provided for such studies, particularly because many manufacturers have requested FDA's guidance in conducting such studies. On that basis, the more detailed version of the guidelines has been retained in § 320.27 of the final regulations and expanded in reply to a number of comments to this section.

39. One comment stated that proposed § 320.2(d)(5)(i) and (vi) and (6)(ii) should be amended to indicate that while single-dose crossover studies should have a drug elimination period, multiple-dose crossover studies should not have a drug elimination period and therefore should be performed under protocols of continuous administration. In support of this statement, the comment noted that once the "steady state" has been achieved by administration of the initial drug, the second drug given should, if equally bioavailable and given at the same dosage, maintain the same levels. If the level of bioavailability being measured either decreases or increases, the two drug formulations are not comparable. The changes in effect would be shown on the crossover with clearer results without a washout period than with such a period. On the other hand, a single-dose study does not achieve a constant level, hence any drug remaining in the test subject can alter the results on crossover. Therefore, single-dose crossover studies should specifically be required to utilize elimination periods unless, for some reason, such a period is not necessary.

The Commissioner agrees that a drug elimination period is not ordinarily required in a multiple-dose study, provided steady-state conditions are achieved. The Commissioner recognizes that, in studies involving drugs having a very long half-life, multiple-dose studies may be unfeasible and/or hazardous, particularly in normal volunteers, where the dosing interval is significantly shorter than the half-life of the drug. Section 320.26(b) of the final regulations states that a drug elimination period should be provided for in a single-dose crossover study. Section 320.27(b) states that a drug elimination period should be provided for in multiple-dose crossover studies if steady-state conditions are not achieved.

40. The Commissioner advises that the guidelines on the design of a single-dose or multiple-dose in vivo bioavailability study in §§ 320.26 and 320.27 of the final regulations are very basic guidelines. They are not intended to include all of the requirements necessary for designing and conducting a bioavailability study. The FDA is preparing detailed guidelines for bioavailability studies that will be available from the Bureau of Drugs, Division of Biopharmaceutics (HFD–520), 5600 Fishers Lane, Rockville, MD 20857. To clarify that the guidelines are not absolute requirements, the word "should" is substituted for "shall" in §§ 320.26 and 320.27 of the final regulations.

41. Proposed § 320.2(d)(5)(vi) stated that the drug elimination period in a single-dose crossover study should be at least five times the half-life of the therapeutic moiety or its metabolite or five times the half-time of decay of the acute pharmacological effect. The Commissioner believes that, because of the limitations of available technology, it may not be possible to monitor the drug elimination period for five half-lives in a single-dose study. Therefore, he is revising § 320.26(b)(2) of the final regulations to state that, unless some other approach is appropriate for valid scientific reasons, the drug elimination period in a single-dose crossover study should be either at least three times the half-life of the active drug ingredient or therapeutic moiety or its metabolite(s), measured in the blood or urine, or at least three times the half-life of decay of the acute pharmacological effect. The Commissioner believes that, with available technology, it is possible to monitor the drug elimination period in a multiple-dose crossover study for at least five half-lives. Therefore, § 320.27(b)(3) of the final regulations states that, if a drug elimination period is required in a multiple-dose study, unless some other approach is more appropriate for valid scientific reasons, the drug elimination period should be either at least five times the half-life of the active drug ingredient or therapeutic moiety, or its metabolite(s), measured in the blood or urine, or at least five times the half-life of decay of the acute pharmacological effect.

42. One comment objected to the statement in proposed § 320.2(d)(6)(i) that multiple-dose studies may be required to determine bioavailability where there is a difference in the rate of absorption but not in the extent of absorption. The comment noted that bioavailability is defined as both the rate and extent of absorption; at steady state, the mean plasma level (Cp mean) will be a function of the extent of absorption only. Where the difference in bioavailability lies with the rate of absorption, the single-dose study is more appropriate. The comment added that this would especially apply to controlled release preparations where the input rate has been deliverately altered. The single-dose study would be more appropriate in following the absorption rate to determine that the controlled release claim for the product was correct.

The Commissioner believes that occasionally there is a need to define maximum (Cmax) and minimum (Cmin) concentrations under steady-state conditions. Multiple-dose studies that define Cmax and Cmin blood concentrations are most appropriate when dealing with drugs possessing a narrow therapeutic ratio, drugs requiring careful patient titration, and controlled release dosage forms. In the case of controlled release dosage forms, it is not sufficient to demonstrate merely the slow release and absorption of the dosage form; both safety and effectiveness of the product must also be demonstrated. The latter requires sufficient proof of reproducibility in release rate; proof is best determined in multiple-dose studies. In addition there is the need to obtain sufficient pharmacokinetic data for purposes of labeling the controlled release dosage form.

43. Two other comments stated that among the instances requiring multiple-dose studies are those where there is excessive variability from subject to subject or where the concentration of the therapeutic moiety in the blood or urine, resulting from a single dose, is too low for accurate anlysis. These comments added that the two instances should be deleted since neither is a valid reason to require multiple-dose studies and accurate results can be achieved by increasing the patient population in the first instance or increasing the dose in single-dose studies in the second instance.

The Commissioner does not agree with these comments. Excessive subject variability and the existence of blood concentration too low for the analytical method may indeed be valid reasons for requiring multiple-dose studies. In many cases, increasing the dose administered may be both hazardous to the subject and not reflective of the absorption pattern of the drug product under question. If there is excessive variability from subject to subject, large numbers of subjects employing single-dose studies would be required to demonstrate bioavailability. In his opinion, such studies are technically unfeasible because of the difficulty of assuring adequate clinical monitoring.

44. Although no comments were received regarding proposed § 320.2(d)(6)(ii), the Commissioner has reviewed this provision and is modifying it to clarify that crossover studies are not required if the purpose of a multiple-dose study is to establish dose proportionality under a multiple-dose regimen or the pharmacokinetic profile of a new drug entity, new drug delivery system, or controlled release dosage form. As revised § 320.27(b)(2) of the final regulations reads: "A multiple-dose study is not required to be of crossover design if the study is to establish dose proportionality under a multiple-dose regimen or to establish the pharmacokinetic profile of a new drug product, a new drug delivery system, or a controlled release dosage form."

45. Although no comments were filed regarding proposed § 320.2(d)(6)(iii), the Commissioner is revising § 320.27(c) of the final regulations to provide for flexibility in protocol design by including the phrase "unless some other approach is more appropriate for valid scientific reasons." As revised, § 320.27(c) reads: "Whenever a multiple-dose study is conducted, unless some other approach is more appropriate for valid scientific reasons, sufficient doses of the test product and reference material should ordinarily be administered in accordance with the labeling to achieve steady-state conditions."

46. One comment regarding proposed § 320.2(d)(6)(iv) stated that the wording of the sentence "A more complete characterization * * * of the total area under the concentration curve" gives the impression that calculation of the area under the concentration curve is required. The comment noted that this is redundant because, if a statistical procedure shows that test and reference material do not differ in rate and extent variables, then there is no need to demonstrate that the areas under the curves of the two materials do not differ. The determination of the rate and extent of absorption is necessary to establish bioavailability, while determining the area under the curve is a necessary but not sufficient requirement for establishing bioavailability.

Proposed § 320.2(d)(6)(iv) encourages, but does not require, a more complete characterization of the blood level or urinary excretion rate during the absorption and elimination phases of a single-dose administered at steady state. The Commissioner encourages such complete characterization to permit estimation of the total area under the concentration-time curves and to obtain pharmacokinetic information, e.g., half-life, or blood clearance, that is essential in preparing adequate labeling for the drug product. The Commissioner has expanded § 320.27(d)(3) of the final regulations to clarify why complete characterization is encouraged.

47. One comment regarding proposed § 320.2(d)(6)(iv) stated that, while a protocol of frequent sampling would be a better estimate of the plasma profile, the area under the concentration-time curve for the dosing interval at steady state is proportional (assuming a linear system) to the fraction of the dose absorbed and thus also to the extent of availability, even when no postabsorptive or elimination phase is seen because of slow absorption relative to the dose interval.

The Commissioner agrees with this comment. These facts have been both kinetically predicted and experimentally demonstrated in the scientific literature. Therefore, the Commissioner is revising § 320.27(e)(2) of the final regulations by adding the following statement: "In a linear system, the area under the blood concentration-time curve during a dosing interval in a multiple-dose steady-state study is directly proportional to the fraction of the dose absorbed and is equal to the corresponding 'zero to infinity' area under the curve for a single-dose study. Therefore, when steady-state conditions are achieved, a comparison of blood concentrations during a dosing interval may be used to define the fraction of the active drug ingredient or therapeutic moiety absorbed." Section 320.27(e)(3) states that other methods based on valid scientific reasons should be used to determine the bioavailability of a drug product having dose-dependent kinetics (nonlinear system).

ANALYTICAL METHODS

48. One comment stated that proposed § 320.2(d)(7) discusses the analytical method used in bioavailability studies to measure acute pharmacological effect or the concentration of the active drug ingredient, therapeutic moiety, or metabolite(s) in body fluids or excretory products. The section omits bioavailability studies conducted with radioactively labeled drugs. As a part of the analytical methodology, the comment suggested that studies conducted with radioactively labeled drugs be included.

In paragraph 14 above, the Commissioner discusses the use of isotopically labeled drugs in a bioavailability study and is amending the final regulations to provide for such use when approved by FDA. The Commissioner, however, concludes that it is unnecessary to amend § 320.29 in the final regulations to refer to the use of radioactively labeled drugs because this section is concerned with the sensitivity of, not the choice of, the analytical method.

49. One comment stated that proposed § 320.2(d)(9) (now § 320.23) contains no mechanism to satisfy the requirement that the bioavailability test shall be of sufficient sensitivity to discriminate between inequivalent products. The comment stated that the requirement implies that a product of known poor bioavailability must be compared against the reference material to determine whether the method can detect differences between the two products.

Statistical analysis of data is the mechanism for determining whether a bioavailability test is sufficiently sensitive to discriminate between inequivalent products. A variety of statistical techniques are available for this analysis, e.g., analysis of variance, student T test, chi square test, and Hottelings' T^2 test. The investigator has to choose from among those many statistical techniques one of sufficient sensitivity to detect differences in bioavailability that are not attributable to subject variability. The statement in proposed § 320.2(d)(9) was not intended to suggest that a product of known poor bioavailability is to be run against the reference material, and, as noted in paragraph 51 below, has been revised.

50. Two comments stated that proposed § 320.2(d)(9) does not distinguish bioavailability from bioequivalence testing. For example, the relationship of a new therapeutic pharmaceutical alternative with comparable labeling should be shown to have comparable rate and extent of absorption to the reference standard, e.g., marketed product. One of the comments added that the phrase "may be considered medically insignificant" appears to be vague. The comments proposed that § 320.2(d)(9) be revised to read: "For new products containing a new therapeutic moiety that has not been previously marketed and for new formulations, new dosage forms, or new salts or esters of an already marketed therapeutic moiety that are to be administered by an alternate route to those of the currently marketed drug products, the drug product shall be shown to be bioavailable by evidence of the rate and extent of absorption, as determined by comparison of measured parameters, e.g., concentrations of the drug in the plasma, urinary excretion rates, pharmacological effects, etc., to those of the reference material. In this case (where bioavailability only is determined) ordinarily the drug product will not be similar in rate and extent of absorption to that of the reference material. For

drug products undergoing testing to determine whether they meet bioequivalence requirements and for new formulations, new dosage forms, or new salts or esters of an already marketed therapeutic moiety that are to be administered by the same route as that of a currently marketed drug product, said drug product(s) shall be deemed to be bioequivalent if the rate and extent of absorption, as determined by measured parameters, e.g., concentrations of the drug in the plasma, urinary excretion rates, pharmacological effects, etc., have comparable location parameters, e.g., means, medians, etc., to those of the reference material, provided that the bioavailability test is sufficiently sensitive to discriminate between specified differences in formulations. A drug product may be equivalent to the reference material in the extent of absorption but not in its rate of absorption and yet may be considered to be bioequivalent because such differences in rate of absorption may be intentional or are not essential to the attainment of effective body drug concentrations on chronic usage."

Another comment recommended that proposed § 320.2(d)(9) be deleted entirely because it confuses the terms bioavailability and bioequivalence. Two other comments stated that the phrase "do not differ significantly" is vague. One of these comments recommended insertion of the word "statistically" before the words "differ significantly."

The Commissioner agrees that proposed § 320.2(d)(9) confuses the terms bioavailability and bioequivalence and that the phrases "do not differ significantly" and "may be considered medically insignificant" need to be clarified. The intent of this section is to provide guidance in evaluating data to determine the bioavailability of a new drug product containing a new therapeutic moiety, or a new dosage form or new salt or ester of an already marketed therapeutic moiety. Therefore, the Commissioner is revising § 320.23 of the final regulations. Under § 320.23 the in vivo bioavailability of a drug product is demonstrated if the product's rate and extent of absorption, as determined by comparison of measured parameters, e.g., concentrations of the active drug ingredient in the blood, urinary excretion rates, or pharmacological effects, do not indicate a significant difference from the reference material's rate and extent of absorption. Statistical techniques used shall be of sufficient sensitivity to detect differences in rate and extent of absorption that are not attributable to subject variability. A drug product that differs from the reference material in its rate of absorption, but not in its extent of absorption, may be considered to be bioavailable if the difference in the rate of absorption is intentional and appropriately reflected in the labeling, and/or not detrimental to the safety and effectiveness of the drug product.

51. One comment noted that proposed § 320.2(d)(9) states that significant differences in rate of absorption will be disregarded in determining bioavailability or bioequivalence if the difference is medically insignificant. The comment added that the principle thus recognized is equally applicable to the extent of absorption and recommended that the third sentence in proposed § 320.2(d)(9) be revised to read: "A drug product may be inequivalent to the reference material in the extent or rate of absorption and yet may be considered to be bioavailable or bioequivalent because such difference may be considered medically insignificant for the particular drug product." Two other comments added that while there are little, if any, data that identify those instances where one can make the judgment that differences in the rate of absorption will not be medically significant, there are data that document or strongly suggest that differences in the rate of absorption of glucocorticoids can result in therapeutic failures.

The Commissioner is of the opinion that a drug product's safety and effectiveness is dependent primarily on its ability to deliver a therapeutic quantity of the drug to the site of action and, thus, the extent of absorption, not the rate of absorption, will determine steady-state concentrations. The Commissioner advises, however, that the rate of absorption must be considered in determining bioavailability unless there are data available to support a determination that the rate of absorption is not essential to the safe and effective use of the drug product.

Submission of Protocols

52. One comment stated that proposed § 320.2(d)(8) (now § 320.30(a) and (b)) "recommends" the submission of proposed protcols for bioavailability studies for FDA review where, assumedly, the submission is not required under proposed § 320.2(e). The comment added that if a protocol is submitted as part of an IND under the provisions of § 312.1(a)(2) (21 CFR 312.1(a)(2)), FDA is supposed to respond within 30 days of receipt of the IND; however, proposed § 320.2(d)(8) contains no similar time provision for what is essentially a voluntary submission. To eliminate unnecessary delays and to encourage submissions under this provision, the comment suggested that the following language be added at the end of proposed § 320.2(d)(8): "Proposed protocols for bioavailability studies submitted under this provision will be reviewed and all substantive comments transmitted in writing to the sender within 30 days of receipt of the proposed protocol by the Food and Drug Administration. If no substantive response is received by the sender within this period, the proposed protocol is deemed approved by the Food and Drug Administration." This concept was supported by two other comments.

The Commissioner agrees that proposed protocols for bioavailability studies should be evaluated by FDA as soon as possible consistent with agency resources and priorities. As noted in the preamble to the proposal, FDA will attempt to evaluate these protocols within 30 days of their receipt. While every effort will be made to complete such evaluations as soon as possible, it is impractical and not in the public interest to encourage hasty or superficial evaluation by establishing a requirement that evaluations of protocols be completed within a specific time. The Commissioner advises that protocols submitted in an IND notice will not receive preferential treatment or be deemed approved if FDA has not responded within 30 days. The sponsor of an IND notice is required under § 312.1 to wait until 30 days after receipt of the notice by FDA before initiating clinical studies. Clinical studies are permitted to begin if FDA does not request the sponsor to withhold or to restrict such studies within 30 days. Important questions regarding safety issues are resolved within 30 days; however, a detailed review of the study protocol takes longer. Therefore, the sponsor cannot assume that a protocol for a bioavailability study submitted in an IND notice is deemed approved if he does not hear from FDA within 30 days.

Sample Source

53. Two comments recommended that proposed § 320.2(d)(9) be revised by adding a new sentence, after the first sentence, to read: "The lots tested for bioequivalence should be representative of a full size production lot."

The Commissioner agrees in part with this comment. Although the drug product tested must be identical to the product intended for marketing and be manufactured using the same equipment and under the same conditions as those used for full-scale production, it is not necessary that samples intended for bioavailability testing be taken from a full size production lot. The Commissioner is including in § 320.25(i)(2) of the final regulations a requirement that samples of the drug product to be tested be manufactured using the same equipment and under the same conditions as those used for full-scale production.

Informed Consent

54. Proposed § 320.2(e)(3) (now § 320.31(c)) requires written informed consent of any subject who participates in a bioavailability study conducted under an IND. Section 320.2(e)(2) (now § 320.31(b)) permits certain bioavailability studies involving marketed drug products to be conducted without submission of an IND, and thus subjects who participate in a study that is not conducted under an IND would not be required to give written informed consent. The Commissioner concludes that although protection of the public health does not require that every bioavailability study involving commercially available drug products be conducted under an IND, written informed consent shall be obtained from all subjects who participate in a bioavailability study. Such subjects will normally be healthy volunteers for whom no health benefit will be achieved by participation in the study. Nonetheless, the subjects are

placing themselves at risk, albeit small, by participation in the study. Protection of these subjects requires that they be adequately informed of this risk and give written consent to participate in the study. The Commissioner is revising § 320.31(d) of the final regulations to require written informed consent of all subjects who participate in a bioavailability study regardless of whether the study is conducted under an IND.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 501, 502, 505, 701(a), 52 Stat. 1041–1042 as amended, 1049–1053 as amended, 1055 (21 U.S.C. 321(p), 351, 352, 355, 371(a))) and under authority delegated to the Commissioner (21 CFR 5.1) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

1. In Part 314, § 314.1 is amended in paragraph (c)(2) by adding a new subitem h to item 12 in Form FD–356H to read as follows:

§ 314.1 Applications.

* * * * *

(c) * * *

(2) * * *

FD–356H * * *

12. * * *

h. In vivo bioavailability data or information to permit waiver of this requirement in accordance with Subpart B of Part 320 (21 CFR Part 320, Subpart B).

* * * * *

2. In Part 320:

a. By adding new paragraph (a) to § 320.1 to read as follows:

§ 320.1 Definitions.

(a) "Bioavailability" means the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action.

* * * * *

b. By adding new Subpart B to read as follows:

Subpart B—Procedures for Determining the Bioavailability of Drug Products

Sec.

320.21 Requirements for submission of in vivo bioavailability data.

320.22 Criteria for waiver of evidence of in vivo bioavailability.

320.23 Basis for demonstrating bioavailability.

320.24 General approaches for determining bioavailability.

320.25 Guidelines for the conduct of an in vivo bioavailability study.

320.26 Guidelines on the design of a single-dose in vivo bioavailability study.

320.27 Guidelines on the design of a multiple-dose in vivo bioavailability study.

320.28 Correlation of bioavailability with an acute pharmacological effect or clinical evidence.

320.29 Analytical methods for an in vivo bioavailability study.

320.30 Inquiries regarding bioavailability requirements and review of protocols by the Food and Drug Administration.

320.31 Applicability of requirements regarding a "Notice of Claimed Investigational Exemption for a New Drug".

AUTHORITY: Secs. 201(p), 501, 502, 505, 701(a), 52 Stat. 1041–1042 as amended, 1049–1053 as amended, 1055 (21 U.S.C. 320(p), 351, 352, 355, 371(a)), unless otherwise noted.

§ 320.21 Requirements for submission of in vivo bioavailability data.

(a) Any person submitting a full or abbreviated new drug application to the Food and Drug Administration after July 7, 1977, shall include in the application either:

(1) Evidence demonstrating the in vivo bioavailability of the drug product that is the subject of the application; or,

(2) Information to permit the Food and Drug Administration to waive demonstration of in vivo bioavailability.

(b) Any person submitting a supplemental application to the Food and Drug Administration after July 7, 1977, shall include in the supplemental application the evidence or information set forth in paragraph (a) of this section if the supplemental application proposes any of the following changes:

(1) A change in the manufacturing process, including a change in product formulation or dosage strength, beyond the variations provided for in the approved application.

(2) A change in the labeling to provide for a new indication for use of the drug product, if clinical studies are required to support the new indication for use.

(3) A change in the labeling to provide for a new dosage regimen or for an additional dosage regimen for a special patient population, e.g., infants, if clinical studies are required to support the new or additional dosage regimen.

(c) The Food and Drug Administration may approve a full or abbreviated new drug application, or a supplemental application proposing any of the changes set forth in paragraph (b) of this section, that does not contain evidence of in vivo bioavailability or information to permit waiver of the requirement for in vivo bioavailability data, if all of the following conditions are met:

(1) The application is under review by the Food and Drug Administration on July 7, 1977.

(2) The application is otherwise approvable.

(3) The applicant agrees to submit, within the time specified by the Food and Drug Administration, either:

(i) Evidence demonstrating the in vivo bioavailability of the drug product that is the subject of the application; or,

(ii) Information to permit the Food and Drug Administration to waive demonstration of in vivo bioavailability.

(d) Evidence demonstrating the in vivo bioavailability of a drug product shall be obtained using one of the approaches for determining bioavailability set forth in § 320.24.

(e) Information to permit the Food and Drug Administration to waive demonstration of in vivo bioavailability shall meet the criteria set forth in § 320.22.

(f) Any person holding an approved full or abbreviated new drug application shall submit to the Food and Drug Administration a supplemental application containing new evidence demonstrating the in vivo bioavailability of the drug product that is the subject of the application if notified by the Food and Drug Administration that:

(1) There are data demonstrating that the dosage regimen in the labeling is based on incorrect assumptions or facts regarding the pharmacokinetics of the drug product and following this dosage regimen could potentially result in subtherapeutic or toxic levels; or,

(2) There are data demonstrating significant intra-batch and batch-to-batch variability, e.g., plus or minus 25 percent in the bioavailability of the drug product.

(g) The requirements of this section regarding the submission of evidence demonstrating in vivo bioavailability apply only to a full or abbreviated new drug application or a supplemental application for a finished dosage formulation.

§ 320.22 Criteria for waiver of evidence of in vivo bioavailability.

(a) Any person submitting a full or abbreviated new drug application, or a supplemental application proposing any of the changes set forth in § 320.21(b), may request the Food and Drug Administration to waive the requirement for the submission of evidence demonstrating the in vivo bioavailability of the drug product that is the subject of the application. A request for waiver shall be submitted with the application. The Food and Drug Administration shall waive the requirement for the submission of evidence of in vivo bioavailability if the drug product meets any of the provisions of paragraph (b), (c), or (d) of this section.

(b) For certain drug products the in vivo bioavailability of the drug product may be self evident or not necessary for the product to achieve any of its intended purposes. The Food and Drug Administration shall waive the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability of the drug product if the product meets one of the following criteria:

(1) The drug product meets both of the following conditions:

(i) It is a solution intended solely for intravenous administration.

(ii) It contains an active drug ingredient or therapeutic moiety in the same solvent and concentration as an intravenous solution that is the subject of an approved full new drug application.

(2) The drug product is a topically applied preparation, e.g., a cream, ointment, or gel, intended for local therapeutic effect.

(3) The drug product is an oral dosage form that is not intended to be absorbed, e.g., an antacid or a radiopaque medium.

(4) The drug product meets both of the following conditions:

(i) It is administered by inhalation as a gas or vapor, e.g., a medicinal or an inhalation anesthetic.

(ii) It contains an active drug ingredient or therapeutic moiety in the same dosage form as a drug product that is the subject of an approved full new drug application.

(5) The drug product meets all of the following conditions:

(i) It is an oral solution, elixir, syrup, tincture, or similar other solubilized form.

(ii) It contains an active drug ingredient or therapeutic moiety in the same concentration as a drug product that is the subject of an approved full new drug application.

(iii) It contains no inactive ingredient that is known to significantly affect absorption of the active drug ingredient or therapeutic moiety.

(c) The Food and Drug Administration shall waive the requirement for the submission of evidence demonstrating the in vivo bioavailability of a solid oral dosage form (other than an enteric coated or controlled release dosage form) of a drug product determined to be effective for at least one indication in a Drug Efficacy Study Implementation notice or which is identical, related, or similar to such a drug product under § 310.6 of this chapter if the drug product is neither one of the following nor an identical, related, or similar drug product under § 310.6 of this chapter:

ANTI-ARRHYTHMICS

Procainamide hydrochloride capsules.
Quinidine polygalacturonate tablets.

ANTI-COAGULANTS

Bishydroxycoumarin tablets and capsules.
Warfarin, sodium and postassium tablets.

ANTI-CONVULSANTS

Ethosuximide capsules.
Ethotoin tablets.
Mephenytoin tablets.
Methsuximide capsules.
Paramethadione capsules.
Phenacemide tablets.
Phensuximide capsules and suspension.
Phenytoin suspension.
Primidone tablets and suspension.
Trimethadione capsules.

ANTI-HYPERTENSIVE DIURETICS

Alseroxylon tablets.
Bendroflumethiazide tablets.
Benzthiazide tablets.
Chlorothiazide tablets.
Deserpidine tablets.
Hydrochlorothiazide tablets.
Hydroflumethiazide tablets.
Methyclothiazide tablets.
Polythiazide tablets.
Quinethazone tablets.
Rauwolfia serpentina tablets.
Rescinnamine tablets.
Reserpine tablets.
Trichlormethiazide tablets.

ANTI-HYPERTENSIVE DIURETICS IN COMBINATION

Chlorothiazide and reserpine tablets.
Hydralazine and reserpine tablets.
Hydralazine hydrochloride and hydrochlorothiazide tablets.
Hydrochlorothiazide and deserpidine tablets.
Hydrochlorothiazide and reserpine tablets.
Hydroflumethiazide and reserpine tablets.
Methyclothiazide and deserpidine tablets.
Reserpine, hydralazine hydrochloride and hydrochlorothiazide tablets.
Spironolactone and hydrochlorothiazide tablets.
Trichloromethiazide and reserpine tablets.

ANTI-INFECTIVES

Nitrofurantoin tablets and suspension.
Salicylazosulfapyridine tablets.
Sulfadiazine sodium bicarbonate suspension.
Sulfadiazine, sulfamethazine, and sulfamerazine (triple sulfa) tablets and suspension.
Sulfadiazine tablets.
Sulfadimethoxine tablets, drops, and suspension.
Sulfamerazine tablets.
Sulfamethoxypyridazine acetyl tablets and suspension.
Sulfaphenazole suspension.
Sulfapyridine tablets.
Sulfisomidine tablets.
Sulfisoxazole acetyl suspension.
Sulfisoxazole tablets.

ANTI-MALARIALS

Pyrimethamine tablets.

ANTI-NEOPLASTICS

Chlorambucil tablets.
Methotrexate tablets.
Triethylene melamine tablets.
Uracil mustard capsules.

ANTI-THYROID

Propylthiouracil tablets.

ANTI-TUBERCULAR

Aminosalicylic acid and isoniazid tablets.
Aminosalicylic acid powder, tablets, and resin.
Aminosalicylic calcium granules, tablets, and capsules.
Aminosalicylic potassium tablets, capsules, and powder.
Aminosalicylic sodium powder, tablets, and granules.
Benzoylpas calcium tablets and powder.
Para-aminosalicylate sodium and isoniazid tablets.
Phenylaminosalicylate powder and tablets.

BRONCHIAL DILATORS

Aminophylline tablets.
Dyphylline tablets.
Oxtriphylline tablets.
Theophylline sodium glycinate tablets.

CARBONIC ANHYDRASE INHIBITORS

Acetazolamide tablets.
Dichlorphenamide tablets.
Ethoxzolamide tablets.
Methazolamide tablets.

CARDIAC GLYCOSIDES

Acetyldigitoxin tablets.

CORTICOIDS

Betamethasone tablets.
Cortisone acetate tablets.
Dexamethasone tablets.
Fludrocortisone acetate tablets.
Fluprednisolone tablets.
Hydrocortisone acetate tablets and powder.
Hydrocortisone tablets.
Methylprednisolone tablets.
Paramethasone acetate tablets.
Prednisolone tablets.
Prednisone tablets.
Triamcinolone tablets.

ESTROGENS

Dienestrol tablets.
Diethylstilbestrol diphosphate tablets.
Diethylstilbestrol tablets.
Ethinyl estradiol tablets.

HYPOGLYCEMICS

Tolbutamide tablets.

MISCELLANEOUS

Imipramine hydrochloride tablets.
Isoproterenol sublingual tablets.
Methyltestosterone tablets.
Probenecid tablets.
Sodium sulfoxone tablets.

THYROID SUPPLEMENT

Liothyronine, sodium tablets.

TRANQUILIZERS

Chlordiazepoxide hydrochloride capsules.
Chlorpromazine tablets.
Fluphenazine hydrochloride tablets.
Perphenazine tablets.
Prochlorperazine tablets.
Promazine tablets.
Promethazine tablets.
Thioridazine tablets.
Trifluoperazine tablets.
Triflupromazine tablets.
Trimeprazine tablets.

VITAMIN K

Menadione tablets.
Phytonadione tablets.

(d) For certain drug products bioavailability may be demonstrated by evidence obtained in vitro in lieu of in vivo data. The Food and Drug Administration shall waive the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability of the drug product if the drug product meets one of the following criteria:

(1) The drug product is subject to a bioequivalence requirement established by the Food and Drug Administration under Subpart C of this Part that specifies only an in vitro testing requirement.

(2) The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product made by the same manufacturer and the following conditions are met:

(i) The bioavailability of this other drug product has been demonstrated.

(ii) Both drug products meet an appropriate in vitro test approved by the Food and Drug Administration.

(iii) The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients.

(3) The drug product is, on the basis of scientific evidence submitted in the application, shown to meet an in vitro test that assures bioavailability, i.e., an in vitro test that has been correlated with in vivo data.

(4) The drug product is a reformulated product that is identical, except for color, flavor, or preservative, to another drug product made by the same manufacturer and both of the following conditions are met:

(i) The bioavailability of the other product has been demonstrated.

(ii) Both drug products meet an appropriate in vitro test approved by the Food and Drug Administration.

(5) The drug product contains the same active drug ingredient or therapeutic moiety and is in the same strength and dosage form as a drug product that is the subject of an approved full or abbreviated new drug application, and both drug products meet an appropriate in vitro test that has been approved by the Food and Drug Administration.

(e) The Food and Drug Administration, for good cause, may defer or waive a requirement for the submission of evidence of in vivo bioavailability if deferral

or waiver is compatible with the protection of the public health.

§ 320.23 Basis for demonstrating bioavailability.

(a) The in vivo bioavailability of a drug product is demonstrated if the product's rate and extent of absorption, as determined by comparison of measured parameters, e.g., concentration of the active drug ingredient in the blood, urinary excretion rates, or pharmacological effects, do not indicate a significant difference from the reference material's rate and extent of absorption.

(b) Statistical techniques used shall be of sufficient sensitivity to detect differences in rate and extent of absorption that are not attributable to subject variability.

(c) A drug product that differs from the reference material in its rate of absorption, but not in its extent of absorption, may be considered to be bioavailable if:

(1) The difference in the rate of absorption is intentional and appropriately reflected in the labeling; and/or

(2) The rate of absorption is not detrimental to the safety and effectiveness of the drug product.

§ 320.24 General approaches for determining bioavailability.

(a) Bioavailability is usually determined by measurement of:

(1) The concentration of the active drug ingredient or therapeutic moiety, or its metabolite(s), in biological fluids as a function of time; or

(2) The urinary excretion of the therapeutic moiety or its metabolite(s) as a function of time; or

(3) An appropriate acute pharmacological effect.

(b) Bioavailability may be determined by several direct or indirect in vivo methods, generally involving testing in humans. The selection of the method depends upon the purpose of the study, the analytical method available, and the nature of the drug product. These limitations affect the degree to which precise pharmacokinetic studies can be applied and, in some cases, necessitate the use of other methods. Bioavailability testing shall be conducted using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (c) of this section.

(c) The following in vivo approaches, in descending order of accuracy, sensitivity, and reproducibility, are acceptable for determining the bioavailability of a drug product.

(1) In vivo testing in humans in which the concentration of the active drug ingredient or therapeutic molety or its metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time, or in which the urinary excretion of the therapeutic moiety, or its metabolite(s), is measured as a function of time. This approach is particularly applicable to dosage forms intended to deliver the active drug ingredient or therapeutic moiety, or to the blood stream for systemic distribution within the body, i.e., injectable drugs, most oral dosage forms, most suppositories, certain drugs administered by inhalation, and some drugs administered by local application to mucous membranes.

(2) In vivo testing in humans in which an appropriate acute pharmacological effect of the active drug ingredient or therapeutic moiety, or metabolite(s), is measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility. This approach is applicable when appropriate methods are not available for measurement of the concentration of the active drug ingredient or therapeutic moiety, or its metabolite(s), in biological fluids or excretory products but a method is available for the measurement of an appropriate acute pharmacological effect. This approach is applicable to the same dosage forms listed in paragraph (c) (1) of this section.

(3) Well-controlled clinical trials in humans that establish the safety and effectiveness of the drug product. This approach is the least accurate, sensitive, and reproducible of the general approaches for determining in vivo bioavailability in humans. For dosage forms intended to deliver the active drug ingredient or therapeutic moiety to the bloodstream for systemic distribution within the body, this approach shall be considered as providing a sufficiently accurate estimate of in vivo bioavailability only when analytical methods are not available to permit use of one of the approaches outlined in paragraph (c) (1) and (2) of this section. This approach shall also be considered as sufficiently accurate for determining the bioavailability of dosage forms intended to deliver the therapeutic moiety locally, e.g., topical preparations for the skin, eye, ear, mucous membranes; oral dosage forms not intended to be absorbed, e.g., an antacid or a radiopaque medium; and bronchodilators administered by inhalation if the onset and duration of pharmacological activity are defined.

(4) Any other in vivo approach approved by the Food and Drug Administration. This provision is intended for special situations and to include those circumstances where the in vivo bioavailability of a drug product might be determined in a suitable animal model rather than in humans or by using a radioactive or nonradioactive isotopically labeled drug product.

§ 320.25 Guidelines for the conduct of an in vivo bioavailability study.

(a) *Guiding principles.* (1) The basic principle in an in vivo bioavailability study is that no unnecessary human research should be done.

(2) An in vivo bioavailability study shall not be conducted in humans if an appropriate animal model exists and correlation of results in animals and humans has been demonstrated. If an appropriate animal model does not exist, however, an in vivo bioavailability study shall ordinarily be done in normal adults under standardized conditions.

(3) In some situations, an in vivo bioavailability study in humans may preferably and more properly be done in suitable patients. Critically ill patients shall not be included in an in vivo bioavailability study unless the attending physician determines that there is a potential benefit to the patient.

(b) *Basic design.* The basic design of an in vivo bioavailability study is determined by the following:

(1) The scientific questions to be answered.

(2) The nature of the reference material and the dosage form to be tested.

(3) The availability of analytical methods.

(4) Benefit-risk considerations in regard to testing in humans.

(c) *Comparison to a reference material.* In vivo bioavailability testing of a drug product shall be in comparison to an appropriate reference material unless some other approach is more appropriate for valid scientific reasons.

(d) *Previously unmarketed active drug ingredients or therapeutic moieties.* (1) The purpose of an in vivo bioavailability study involving a drug product containing an active drug ingredient or therapeutic moiety that has not been approved for marketing is to determine:

(i) The bioavailability of the formulation proposed for marketing; and

(ii) The essential pharmacokinetic characteristics of the active drug ingredient or therapeutic moiety, such as the rate of absorption, the extent of absorption, the half-life of the therapeutic moiety in vivo, and the rate of excretion and/or metabolism. Dose proportionality of the active drug ingredient or the therapeutic moiety needs to be established after single-dose administration and in certain instances after multiple-dose administration. This characterization is a necessary part of the investigation of the drug to support drug labeling.

(2) The reference material in such a bioavailability study should be a solution or suspension containing the same quantity of the active drug ingredient or therapeutic moiety as the formulation proposed for marketing.

(3) The reference material should be administered by the same route as the formulation proposed for marketing unless an alternative or additional route is necessary to answer the scientific question under study. For example, in the case of an active drug ingredient or therapeutic moiety that is poorly absorbed after oral administration, it may be necessary to compare the oral dosage form proposed for marketing with the active drug ingredient or therapeutic moiety administered in solution both orally and intravenously.

(e) *New formulations of active drug ingredients or therapeutic moieties approved for marketing.* (1) The purpose of an in vivo bioavailability study involving a drug product that is a new formulation, a new dosage form, or a new salt or ester of an active drug ingredient or therapeutic moiety that has been approved for marketing is to:

(i) Determine the bioavailability of the new formulation, new dosage form, or new salt or ester relative to an appropriate reference material; and

(ii) Define the pharmacokinetic parameters of the new formulation, new dosage form, or new salt or ester to estabilsh dosage recommendation.

(2) The selection of the reference material(s) in such a bioavailability study depends upon the scientific questions to be answered, the data needed to establish comparability to a currently marketed drug product, and the data needed to establish dosage recommendations.

(3) The reference material should be taken from a current batch of a drug product that is the subject of an approved new drug application and that contains the same active drug ingredient or therapeutic moiety, if the new formulation, new dosage form, or new salt or ester is intended to be comparable to or to meet any comparative labeling claims made in relation to the drug product that is the subject of an approved new drug application.

(f) *Controlled release formulations.* (1) The purpose of an in vivo bioavailability study involving a drug product for which a controlled release claim is made is to determine if all of the following conditions are met:

(i) The drug product meets the controlled release claims made for it.

(ii) The bioavailability profile established for the drug product rules out the occurrence of any dose dumping.

(iii) The drug product's steady-state performance is equivalent to a currently marketed noncontrolled release or controlled release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application.

(iv) The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

(2) The reference material(s) for such a bioavailability study shall be chosen to permit an appropriate scientific evaluation of the controlled release claims made for the drug product. The reference material shall be one of the following or any combination thereof:

(i) A solution or suspension of the active drug ingredient or therapeutic moiety.

(ii) A currently marketed noncontrolled release drug product containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling of the noncontrolled release drug product.

(iii) A currently marketed controlled release drug product subject to an approved full new drug application containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling proposed for the controlled release drug product.

(iv) A reference material other than one set forth in paragraph (f)(2)(i), (ii) or (iii) of this section that is appropriate for valid scientific reasons.

(g) *Combination drug products.* (1) Generally, the purpose of an in vivo bioavailability study involving a combination drug product is to determine if the rate and extent of absorption of each active drug ingredient or therapeutic moiety in the combination drug product is equivalent to the rate and extent of absorption of each active drug ingredient or therapeutic moiety administered concurrently in separate single-ingredient preparations.

(2) The reference material in such a bioavailability study should be two or more currently marketed, single-ingredient drug products each of which contains one of the active drug ingredients or therapeutic moieties in the combination drug product. The Food and Drug Administration may, for valid scientific reasons, specify that the reference material shall be a combination drug product that is the subject of an approved new drug application.

(3) The Food and Drug Administration may permit a bioavailability study involving a combination drug product to determine the rate and extent of absorption of selected, but not all, active drug ingredients or therapeutic moieties in the combination drug product. The Food and Drug Administration may permit this determination if the pharmacokinetics and the interactions of the active drug ingredients or therapeutic moieties in the combination drug product are well known and the therapeutic activity of the combination drug product is generally recognized to reside in only one of the active drug ingredients or therapeutic moieties, e.g., ampicillin in an ampicillin-probenecid combination drug product.

(h) *Use of a placebo as the reference material.* Where appropriate or where necessary to demonstrate the sensitivity of the test, the reference material in a bioavailability study may be a placebo if:

(1) The study measures the therapeutic or acute pharmacological effect of the active drug ingredient or therapeutic moiety; or

(2) The study is a clinical trial to establish the safety and effectiveness of the drug product.

(i) *Standards for test drug product and reference material.* (1) Both the drug product to be tested and the reference material, if it is another drug product, shall be shown to meet all compendial or other applicable standards of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and dissolution rates.

(2) Samples of the drug product to be tested shall be manufactured using the same equipment and under the same conditions as those used for full-scale production.

§ 320.26 Guidelines on the design of a single-dose in vivo bioavailability study.

(a) *Basic principles.* (1) An in vivo bioavailability study should be a single-dose comparison of the drug product to be tested and the appropriate reference material conducted in normal adults.

(2) The test product and the reference material should be administered to subjects in the fasting state, unless some other approach is more appropriate for valid scientific reasons.

(b) *Study design.* (1) A single-dose study should be crossover in design, unless a parallel design or other design is more appropriate for valid scientific reasons, and should provide for a drug elimination period.

(2) Unless some other approach is appropriate for valid scientific reasons, the drug elimination period should be either:

(i) At least three times the half-life of the active drug ingredient or therapeutic moiety, or its metabolite(s), measured in the blood or urine; or

(ii) At least three times the half-life of decay of the acute pharmacological effect.

(c) *Collection of blood samples.* (1) When comparison of the test product and the reference material is to be based on blood concentration time curves, unless some other approach is more appropriate for valid scientific reasons, blood samples should be taken with sufficient frequency to permit an estimate of both:

(i) The peak concentration in the blood of the active drug ingredient or therapeutic moiety, or its metabolite(s), measured; and

(ii) The total area under the curve for a time period at least three times the half-life of the active drug ingredient or therapeutic moiety, or its metabolite(s), measured.

(2) In a study comparing oral dosage forms, the sampling times should be identical.

(3) In a study comparing an intravenous dosage form and an oral dosage form, the sampling times should be those needed to describe both:

(i) The distribution and elimination phase of the intravenous dosage form; and

(ii) The absorption and elimination phase of the oral dosage form.

(4) In a study comparing drug delivery systems other than oral or intravenous dosage forms with an appropriate reference standard, the sampling times should be based on valid scientific reasons.

(d) *Collection of urine samples.* When comparison of the test product and the reference material is to be based on cumulative urinary excretion-time curves, unless some other approach is more appropriate for valid scientific reasons, samples of the urine should be collected with sufficient frequency to permit an estimate of the rate and extent of urinary excretion of the active drug ingredient or therapeutic moiety, or its metabolite(s), measured.

(e) *Measurement of an acute pharmacological effect.* (1) When comparison of the test product and the reference material is to be based on acute pharmacological effect-time curves, measurements of this effect should be made with sufficient frequency to permit a reasonable estimate of the total area under the curve for a time period at least three times the half-life of decay of the pharmacological effect, unless some other approach is more appropriate for valid scientific reasons.

(2) The use of an acute pharmacological effect to determine bioavailability may further require demonstration of dose-related response. In such a case, bioavailability may be determined by comparison of the dose-response curves as well as the total area under the acute pharmacological effect-time curves for any given dose.

§ 320.27 Guidelines on the design of a multiple-dose in vivo bioavailability study.

(a) *Basic principles.* (1) In selected circumstances it may be necessary for the test product and the reference material to be compared after repeated administration to determine steady-state levels of the active drug ingredient or therapeutic moiety in the body.

(2) The test product and the reference material should be administered to subjects in the fasting or nonfasting state, depending upon the conditions reflected in the proposed labeling of the test product.

(3) A multiple-dose study may be required to determine the bioavailability of a drug product in the following circumstances:

(i) There is a difference in the rate of absorption but not in the extent of absorption.

(ii) There is excessive variability in bioavailability from subject to subject.

(iii) The concentration of the active drug ingredient or therapeutic moiety, or its metabolite(s), in the blood resulting from a single dose is too low for accurate determination by the analytical method.

(iv) The drug product is a controlled release dosage form.

(b) *Study design.* (1) A multiple-dose study should be crossover in design, unless a parallel design or other design is more appropriate for valid scientific reasons, and should provide for a drug elimination period if steady-state conditions are not achieved.

(2) A multiple-dose study is not required to be of crossover design if the study is to establish dose proportionality under a multiple-dose regimen or to establish the pharmacokinetic profile of a new drug product, a new drug delivery system, or a controlled release dosage form.

(3) If a drug elimination period is required, unless some other approach is more appropriate for valid scientific reasons, the drug elimination period should be either:

(i) At least five times the half-life of the active drug ingredient or therapeutic moiety, or its metabolite(s), measured in the blood or urine; or

(ii) At least five times the half-life of decay of the acute pharmacological effect.

(c) *Achievement of steady-state conditions.* Whenever a multiple-dose study is conducted, unless some other approach is more appropriate for valid scientific reasons, sufficient doses of the test product and reference material should be administered in accordance with the labeling to achieve steady-state conditions.

(d) *Collection of blood or urine samples.* (1) Whenever comparison of the test product and the reference material is to be based on blood concentration-time curves at steady-state, sufficient samples of blood should be taken to define adequately the maximum (Cmax) and minimum (Cmin) blood concentrations on 2 or more consecutive days to establish that steady-state conditions are achieved.

(2) Whenever comparison of the test product and the reference material is to be based on cumulative urinary excretion-time curves at steady-state, sufficient samples of urine should be taken to define the rate and extent of urinary excretion on 2 or more consecutive days to establish that steady-state conditions are achieved.

(3) A more complete characterization of the blood concentration or urinary excretion rate during the absorption and elimination phases of a single dose administered at steady-state is encouraged to permit estimation of the total area under concentration-time curves or cumulative urinary excretion-time curves and to obtain pharmacokinetic information, e.g., half-life or blood clearance, that is essential in preparing adequate labeling for the drug product.

(e) *Steady-state parameters.* (1) In certain instances, e.g., in a study involving a new drug entity, blood clearances at steady-state obtained in a multiple-dose study should be compared to blood clearances obtained in a single-dose study to support adequate dosage recommendations.

(2) In a linear system, the area under the blood concentration-time curve during a dosing interval in a multiple-dose steady-state study is directly proportional to the fraction of the dose absorbed and is equal to the corresponding "zero to infinity" area under the curve for a single-dose study. Therefore, when steady-state conditions are achieved, a comparison of blood concentrations during a dosing interval may be used to define the fraction of the active drug ingredient or therapeutic moiety absorbed.

(3) Other methods based on valid scientific reasons should be used to determine the bioavailability of a drug product having dose-dependent kinetics (nonlinear system).

(f) *Measurement of an acute pharmacological effect.* When comparison of the test product and the reference material is to be based on acute pharmacological effect-time curves, measurements of this effect should be made with sufficient frequency to demonstrate a maximum effect and a lack of significant difference between the test product and the reference material.

§ 320.28 Correlation of bioavailability with an acute pharmacological effect or clinical evidence.

Correlation of in vivo bioavailability data with an acute pharmacological effect or clinical evidence of safety and effectiveness may be required if needed to establish the clinical significance of a special claim, e.g., in the case of a controlled release preparation.

§ 320.29 Analytical methods for an in vivo bioavailability study.

(a) The analytical method used in an in vivo bioavailability study to measure the concentration of the active drug ingredient or therapeutic moiety, or its metabolite(s), in body fluids or excretory products, or the method used to measure an acute pharmacological effect shall be demonstrated to be accurate and of sufficient sensitivity to measure, with appropriate precision, the actual concentration of the active drug ingredient or therapeutic moiety, or its metabolite(s), achieved in the body.

(b) When the analytical method is not sensitive enough to measure accurately the concentration of the active drug ingredient or therapeutic moiety, or its metabolite(s), in body fluids or excretory products produced by a single dose of the test product, two or more single doses may be given together to produce higher concentration if the requirements of § 320.31 are met.

§ 320.30 Inquiries regarding bioavailability requirements and review of protocols by the Food and Drug Administration.

(a) The Commissioner of Food and Drugs strongly recommends that, to avoid the conduct of an improper study and unnecessary human research, any person planning to conduct a bioavailability study submit the proposed protocol for the study to the Food and Drug Administration for review prior to the initiation of the study.

(b) The Food and Drug Administration shall review a proposed protocol for a bioavailability study and determine if all of the following conditions are met:

(1) The design of the proposed bioavailability study is appropriate.

(2) The reference material to be used in the bioavailability study is appropriate.

(3) The proposed chemical and statistical analytical methods are adequate.

(c) General inquiries relating to in vivo bioavailability requirements and methodology shall be submitted to the Food and Drug Administration, Bureau of Drugs, Division of Biopharmaceutics (HFD–520), 5600 Fishers Lane, Rockville, MD 20857.

§ 320.31 Applicability of requirements regarding a "Notice of Claimed Investigational Exemption for a New Drug."

(a) Any person planning to conduct an in vivo bioavailability study in humans shall submit a "Notice of Claimed Investigational Exemption for a New Drug" if either:

(1) The test product contains a new chemical entity that is not the subject of an approved new drug application; or

(2) The study involves a radioactively labeled drug product.

(b) Any person planning to conduct a bioavailability study in humans using a currently commercially available drug product that is the subject of an ap-

proved new drug application, or is identical, similar, or related to such a drug product shall submit an IND if the study is one of the following:

(1) A single-dose study in normal subjects or patients where the dose exceeds that specified in the labeling of the drug product that is the subject of an approved new drug application.

(2) A multiple-dose study in patients where the dose exceeds that specified in the labeling of the drug product that is the subject of an approved new drug application.

(3) A multiple-dose study in normal subjects whether or not the dose exceeds that specified in the labeling of the drug product that is the subject of an approved new drug application.

(c) The provisions of § 312.1 of this chapter are applicable to any bioavailability study conducted under a "Notice of Claimed Investigational Exemption for a New Drug."

(d) The consent of all human subjects (or their representatives) who participate in a bioavailability study (regardless of whether the study is conducted under a "Notice of Claimed Investigational Exemption for a New Drug") shall be obtained in writing under § 310.102 of this chapter.

Effective date: This regulation shall be effective July 7, 1977.

(Secs. 201(p), 501, 502, 505, 701(a), 52 Stat. 1041–1042 as amended, 1049–1053 as amended, 1055 (21 U.S.C. 321(p), 351, 352, 355, 371(a)))

Dated: December 30, 1976.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

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